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INTRODUCTION OF THE JANEWAY LECTURER

By H. DABNEY KERR, M.D.

Doctor Schulz, Doctor Failla, Ladies and Gentlemen:

To introduce the man who is to speak to us this afternoon requires perusal of a great deal of material because of his tremendous experience and the accomplishments credited to his name. He was born many years ago in Texas. He took his medical training in Chicago and while still a medical student began his work with the x-ray. I say "x-ray" advisedly because it was hardly the custom to speak of the roentgen ray. As a student one of the first things he did was to repeat many of the experiments of Dr. Walter Cannon in his basic observations on the digestive tract. He graduated in 1905 and from then on his work in radiology has been nothing short of phenomenal. There is so much that could be said about our speaker this afternoon that I really could give you a lecture on him, but this is not the appropriate occasion.

I, therefore, would like principally to emphasize a certain category, and mention things in which he has been outstanding. Before many in this room were even born he had published a four-volume x-ray atlas on "Roentgen Diagnosis of the Digestive Tract." Most of that work still stands as truths confirmed many times. His work in publications has been extraordinary. There is no need to remind this audience of the work he has done in the translation of many of the important works of foreign authors. Those of us who are not as well acquainted with foreign languages as we should be are still not caught short since through his efforts have had this material available to us. Editorially, also, he had the distinction of being for several years editor of the AMERICAN JOURNAL OF ROENTGENOLOGY, *and of sixteen volumes of the Annals of Roentgenology.*

During the First World War he served in France as the Director of the X-ray Service of the American Expeditionary Forces in France and England, and this post he held until the arrival of Colonel Christie, shortly before the Armistice.

His academic work began in 1912 when he installed the department and was made lecturer in radiology at Northwestern University Medical School. In 1915 he was made professor and kept this post until 1947 when he reached the age of retirement.

During all these years he made many trips to Europe to study under the most distinguished men of the day in England, France, Germany, Austria—the names are very familiar. He was on intimate speaking terms with all of them. He made four or five trips to Central and South America, and it is in this region where he has been a real ambassador of radiologic good will from the United States. I could go on at considerable length about the things he has accomplished. He was the first man to use 200 kv. x-ray. He was one of the early men to use an appreciable amount of radium. His work and distinction have been recognized by many societies. He is an honorary member of various radiologic societies—Britain, France, Sweden, Austria, Germany, Spain, the Argentine, Perú, Cuba, México, and others, not to mention those in our own country. At the most recent of the Inter-American Congresses of Radiology held at Lima, Perú, in 1958 he was given a silver platter with the inscription in Spanish "From the Sixth Inter-American Congress of Radiology to Dr. James T. Case, Ambassador of Radiology in America."

I am now privileged to introduce to you a past president of the American Roentgen Ray Society, a past president of the American College of Radiology, a past president of the American Radium Society, Caldwell Lecturer of the American Roentgen Ray Society, which he established during his presidency, Carman Lecturer of the Radiological Society of North America, and now Janeway Lecturer of the American Radium Society, Dr. James T. Case!

THE EARLY HISTORY OF RADIUM THERAPY AND THE AMERICAN RADIUM SOCIETY*

JANEWAY LECTURE, 1959

By JAMES T. CASE, M.D.
SANTA BARBARA, CALIFORNIA

THE Janeway lecturers have all been physicians or physicists of notable scientific stature and their contributions represent milestones marking the progress of radium. It is with a profound sense of inadequacy and a definite feeling of presumption that I rise to give the twenty-fourth Janeway Lecture. I appreciate keenly the honor of having received the invitation. My offering relates some of the familiar history of the early applications of radium in surgery and medicine, together with some, perhaps interesting, sidelights not generally known. An effort will also be made to include the story of the evolution of the American Radium Society and some notes about a few of the charter members.

Doctor Janeway was a man of unusual character and accomplishments. I had only a slight personal acquaintance with him, though his teachings were very familiar. I would also like to pay tribute to Burton J. Lee, our 1933 President, who was chiefly responsible for the establishment of the Janeway Lectures. I was associated with Doctor Lee for a short period in France during the First World War while he was attached as Consultant in Surgery to the Second Division and while I was the Senior Consultant in Roentgenology for the American Expeditionary Forces.

Doctor Janeway's work spoke for itself. Through his own efforts and with the co-operation of those around him, especially Drs. Ewing, Quick, Failla and Quimby, he was in a large way responsible for placing the medical applications of radium on a sound basis, and providing an example on which radium therapeutic practice throughout the country was widely patterned. Janeway was noted for his efforts to standardize dosage and render the application of radium more accurate. He was especially prominent for his early attempts to treat carcinoma, particularly uterine carcinoma, and as the first in America to use radium emanation buried in malignant growths.

The first Janeway Lecture was delivered by Dr. James Ewing of New York at the Eighteenth Annual Session of the American Radium Society in Chicago in 1933. Today is the twenty-fourth time the Janeway Lecture has been on the program of our Society. Some interruptions occurred during World War II.

A great deal has already been published in the American Journal of Roentgenology, Radium Therapy and Nuclear Medicine and elsewhere concerning the history of radium, particularly Edith Quimby's outstanding story about "Fifty Years of Radium." Also the biographic work of Eve Curie about her mother presents a true history, excellently documented; I am assured by reliable friends in Paris that her account of the scientific work of the Curies has the approval of high French scientific circles. It is an imposing story, well worth re-reading from time to time, and recommendable as required reading for residents in radiotherapy. The highly interesting contributions by Burnam, Bowing, Fricke, K. S. Davis, and O'Brien constitute a detailed history of the early days of therapeutic radiology. By careful search of the literature we have found it possible to add some revealing sidelights and background material which I hope will prove to be of interest to this audience.

My own connection with radium began about 1913, ten years after my first amateurish efforts with the x-rays while still a medical student. Some of this story, together with a brief record of the beginnings of the American Radium Society, was offered to this organization after the annual banquet at the St. Louis meeting in 1953, and published as an editorial in this Journal. As editorial matter it failed to become included in the general index, so that as

* Presented at the Forty-first Annual Meeting of the American Radium Society, Hot Springs, Virginia, April 6–8, 1959.

historical material it was really buried there. I will therefore attempt to elaborate considerably upon those brief notes.

My early supply of 50 mg. of radium from Vienna was soon increased until we had at the Battle Creek Sanitarium a little more than 600 mg., of which I was made custodian. My decisions as to dosage and technique of application were based on my reading of the scanty literature, as there was no one else in our vicinity using radium at that time, and on help gained by visits to the Kelly Clinic and to the Memorial Hospital in New York.

The discovery of radium and the therapeutic use of radium and radon were closely related to the evolution of roentgen therapy. In the spring of 1896 shortly after the publication of Röntgen's first paper, Becquerel announced that, in addition to fluorescence, compounds of uranium gave off invisible penetrating radiation; subsequently he observed that besides the photographic effect these rays could discharge an electroscope. He also found that this radiation was the property of all compounds of uranium.

Marie Sklodowska's heroic struggle to reach Paris and to acquire her preliminary degrees is a familiar story. She passed her Master's examination in physics in 1893, and in mathematics in 1894. On July 26, 1895 she married Pierre Curie to whom she bore two daughters, Irene in September, 1897 and Eve in December, 1904.

Back at her laboratory at the end of 1897, only three months after Irene's birth, when seeking a subject for research for her doctor's degree, she and her husband were attracted by the work of Becquerel whose experimental studies had been published the previous year. They selected for her thesis an investigation of the origin of the radiant energy which uranium constantly gave off in the form of radiation and the nature of the radiation. Pierre finally was able to arrange for her the free use of a comfortless small glassed-in studio, with little protection against the weather and only rudimentary technical equipment. She soon determined that the amount of activity in a compound of uranium was in exact proportion to the amount of uranium contained. She studied all the elements then known to determine if there were atoms other than the uranium atom which gave off radiations, but found them only in uranium and in thorium. (Edith Quimby calls attention to the fact that Madame Curie coined the word "radioactivity" to describe or define this phenomenon.) By exclusion, she arrived at the decision that this radioactive phenomenon was due to a new element. Pierre Curie in the realization of the amazing character of his wife's experiments, put aside his work on crystals to join with her in the search for the new substance. This partnership endured until Pierre's accidental death years later. The trials, the hardships, the unselfish dogged devotion to science, the deliberate neglect to secure material benefits from their discoveries all appeal to the scientific mind and are very refreshing.

Soon they discovered that pitchblende contained two radioactive elements, the first of which was named polonium, the second, radium. Considerable quantities of pitchblende were obtained from Austria, but to work it necessitated larger quarters. The only structure obtainable was a shed in the Rue Lhomond across the courtyard from the dismal laboratory where Marie had thus far carried on her investigations. It was even more uncomfortable and devoid of conveniences—just a large wooden shed with a bituminous floor, a leaky glass roof, and a defective cast iron stove. But here they triumphed in the isolation of radium and in determining its atomic weight, a final proof demanded by their skeptical physicist and chemist colleagues before they would believe that there was really a new element, radium. Madame Curie then devoted her efforts principally to the preparation of pure radium salts, while her husband continued to study the properties of radium. In 1903, along with Becquerel, they received jointly the Nobel Prize for Physics.

In later years, speaking of the shed in which they had worked, Madame Curie said: "It is true that the discovery of radium was made under difficult circumstances and the hangar that housed it has been invested with the charm of legend. But this romantic element was no advantage; it consumed our strength and retarded results. With better means at our disposal the first five years of our work would have been reduced to two, and our tensions would have been eased." And in 1921 while in the United States to receive a gift of one gram of radium, in an address at Vassar College, she remarked: "The work was one of pure science, and this is a proof that scientific work must not be considered from the point of view of the direct usefulness of it. It must be done for itself, for the beauty of science, and then there is always a chance that a scientific discovery may become, like that of radium, a benefit for humanity."

Pierre Curie died in a traffic accident in 1906. In 1907, Madame Curie, who had succeeded her husband as Professor of Physics at the Sorbonne, prepared a very small quantity of pure radium chloride, from which she again determined accurately the atomic weight of radium; in 1910 she isolated the material, and in 1911 the tube containing 22 mg. which she prepared as a standard was placed in the International Bureau of Weights and Measures in France. This standard has served all the world since then. In this same year, she received a second Nobel Prize for her work. Not all of us realize that the recorded technical procedures by which Madame Curie step by step achieved her goal of preparing the radium salts and finally pure radium were made available to the firms engaging in the commercial production and sale of radium. And this information was freely given without any pecuniary benefits reserved to herself or her family.

The first article on radium which I could find in the *Archives of the Roentgen Ray* appeared in the April, 1903 issue. It asked, "What is the use of all this?" referring to radium. The answer was, "What is the use of a baby? As a baby, it is not of any use; in fact, it is a nuisance. But it will grow into a man who is of use. . . . In the same way it is not easy to say that radium is at present of any use from a strictly practical standpoint. . . . If we had plenty of it we might paint London with calcium sulphide, put radium in all the street lamps, and get a mild moonlight everywhere, thus saving on gas and electricity; but people careful of their complexions might object to its effect on the cuticle."

Just as with the roentgen rays, it was only natural that in the early days of radium there were some curious, ignorant, and fantastic ideas about the strange new substance and attempts to exploit it commercially. For example, "Radiumite" was advertised in 1903 as "nature's gift to mankind. . . . The mysteries of its powers puzzle and bewilder scientists. . . . Keeps you well when you carry it." Directions for using Radiumite were to "put one or two pieces of radium in your pocket or encase it in a silken or chamois skin bag and wear it around the waist or suspend it from the neck." Naturally, tests made by the United States Department of Agriculture of this fraudulent substance showed that it possessed no radioactivity.

Another advertisement from *Medical Age* stated that "cotton wool exposed to radium constituted a convenient means for the distribution of radiation over the surface of the body. The exposed cotton wool could be packed in hermetically sealed jars, where it would lose its activity very slowly, and could be sent to any distance desired." It was thought it might become a stock pharmaceutical preparation.

Medical Record of 1905, page 502, in a news note related that a Doctor Kane and his assistant were sentenced to four years and ten months each in the penitentiary for obtaining $10,000 for an alleged radium cure in which no radium had been used.

It was suggested by Moffett, a science reporter, that the two main causes of fraud "are a widespread credulity in a 'skeptical

age' and a tendency to confuse what may be with what is." There were various proposals for the cure of consumption and cancer, liquid air, with a perpetual motion attachment, and a "distance-see-er" that would "transmit vision over wires and allow anxious wives in Cincinnati to actually see their husbands in New York." One shrewd speculator in human misery proposed to start a radium consumption farm where he would advertise to do wonders for affected lungs by inhalation of radioactive air, for handsome fees.

Moffett also about 1903 told of attending a "radium dinner" given at the Massachusetts Institute of Technology, where the invitations told the guests they would see the latest wonders of radium, including radium cocktails, radium paint, and a perpetual motion machine driven by the tireless energy of radium. "The radium paint turned out to be a joke—just old-fashioned luminous paint with no radium in it. The one hundred fifty radium cocktails (tiny tubes of low-grade radium in glasses) gave less light when the room was darkened than half a dozen healthy fireflies. The perpetual motion machine was 'stuck'. "

He also reported a Russian scientist as suggesting that radium would shortly end wars, since it might explode battleships from the shore. A Paris doctor was sure radium would prove to be a cure for many types of blindness. Another scientist declared that the radium phenomenon would overthrow the atomic theory, and still another that it would make possible transmutation of metals.

In reviewing the somewhat fantastic thoughts just expressed, it is remarkable how many of them suggest a number of the present-day developments of electronics and nuclear science.

There were also accounts of radium losses, one of which is especially interesting. Robert Abbe in *Medical Record*, April 21, 1906, stated that in March, 1906 a small glass tube containing 50 mg. of "pure" radium bromide of the strength 1,800,000, hermetically sealed, on being removed from a silver tube by a thread tied about it, became stuck in the opening of the tube. He pressed it lightly with the end of a metal forceps and instantly it exploded with a loud report, the glass being shattered into numerous small fragments and much of the radium being distributed against the inner lining of the tube. At the same instant he saw a cloud of pulverized radium come from the tube, a cloud as large as his hand, and rather rapidly fall to the carpet, a distance of 1 meter. He marked out on the carpet an outline of the area in which he supposed the powder had fallen, though none of it was visible. With photographic plates he located by autoradiographs the exact spot on the carpet where the radium had fallen, finding that it lay within a small radius of 35 cm., having been kept together by its heaviness. He carefully cut out the piece of carpet, and found it possible to recover the entire specimen.

A similar accident occurring in November, 1905 had been described by Julius Sprecht of the Institute of Technology in Hanover (*Physikalische Zeitschrift*, January 15, 1906), in which a small tube which had been alternately cooled and warmed in a colorimeter experiment spontaneously suddenly exploded while lying undisturbed in a wooden dish, three minutes after bringing it into the air from the instrument.

With our present-day knowledge it is difficult for us to picture the wonderment with which the early news of radium was received in scientific circles throughout the world. In England, for instance, at a meeting of the British Association for the Advancement of Science, September 9, 1903, the president spoke on radium, characterizing its properties as transcending all others in their intrinsic importance and revolutionary possibilities. The discovery by Professor and Madame Curie was so amazing that when he had seen the heated thermometer he was hardly able to believe what he had seen. This discovery which could barely be distinguished from that of perpetual motion, which it was an axiom of science to call impossible, had left every chemist and

physicist in a state of bewilderment. "Further," he said, "Sir William Crookes has devised an experiment in which a particle of radium kept a screen bombarded forever, each collision producing a microscopic flash of light, the dancing and multitude of which forcibly compelled the imagination to follow the reasoning faculties and realize the existence of 'atomic tumult'."

Rutherford remarked that thorium or uranium, which acted in the same kind of way, but with far less vigor, would last a million years; while radium, preferring a short life and a merry one, could not expect to exist for more than a few thousand years. After mentioning the chief physiologic effects of radium then known, effects on the skin producing inflammation and ulcers, effects on the nervous system producing paralysis and death, and luminous effects produced in the partially blind, Dawson Turner remarked, "We may speculate on the uses to which radium may be put . . . patients could be provided with a fragment of radium sealed in a tube which they could themselves apply as directed . . . a small receptacle of radium in a house would warm it by day and light it at night."

In a lecture delivered before the American Institute of Electrical Engineers and the American Chemical Society, April 17, 1903, W. J. Hammer related that Professor Curie had told him that he would not trust himself in a room with a kilogram of pure radium, as it would burn all the skin off his body, destroy his eyesight and probably kill him; also that in recent experiments by Professor Curie, a few milligrams of radium introduced beneath the skin near the vertebral column of a mouse produced death by paralysis within three hours.

* * *

France was the birthplace of radium and it also was the birthplace of radium therapy. Becquerel appears to have been the first to sustain a "radium burn." He carried a glass tube containing 200 mg. of radium in his vest pocket; fifteen days later he found it had caused a reaction on his abdomen which required a month to heal, and led him to remark, "I love this radium, but I've got a grudge against it." Pierre Curie intentionally produced a similar "burn" on his arm. In 1900 Walkoff and Giesel announced that radium had certain physiologic properties.

These demonstrations initiated a series of animal experiments with radium and the beginning of its use on human beings in certain skin diseases. Danlos and Block at Hôpital Saint Louis in Paris first used it in 1901 in the treatment of lupus, reporting in 1902. Danysz attempted to treat malignant disease with radium in 1903. In 1906, a center for the study of radium therapy called the Biological Laboratory of Radium was established in Paris by Wickham and Degrais, who placed Dominici in charge of the clinical work. The activity in this important radium center was the principal influence in countering the disappointment which had followed the preliminary enthusiasm for the use of radium, thereby starting it on a high scientific plane. The scientific explanation of its therapeutic value may be said to have begun in France by the work of Wickham and Degrais. Prior to this time the use of radium in deep-seated cancer had been tried, but success was achieved only in some of the more superficial lesions. Wickham first employed filters with radium to modify the dosage in the deeper tissues, using cotton wool wrapped in goldbeater's skin and in layers of aluminum; he also claimed to have originated the principle of crossfiring, used in 1905 in treating sciatic pain, though Perthes reported its use with roentgen rays in 1904.

But also outside of France physicians everywhere were commencing to use radium therapeutically. William Rollins of Boston in January, 1902 wrote on "Radioactive Substances in Therapeutics," probably the first American medical communication dealing with radium as a therapeutic agent. The London *Lancet* announced on November 14, 1903 that a quantity of "pure radium" had been generously placed at the disposal of a member of the staff of

the Cancer Hospital, Fulham Road, London, S.W. Fricke is the author of the statement that the beginnings of the Holt Radium Institute at Manchester dated from 1905. A radium center was established at Trieste in 1904. The development of radiotherapy in Germany occurred more slowly than in France through "negative skepticism," but this slow start was more than compensated, beginning in 1913, with the work of outstanding gynecologists, like Krönig, Böhm, Döderlein, Gauss, Warnekros, and others. A radium station was founded in Vienna in 1914, following the impressive German successes in the treatment of uterine cancer.

Margaret Cleaves was apparently the first to make an intrauterine application of radium (1903). Joseph G. Beck of Chicago experimented with radium in some nose, throat and ear diseases and published the results in December, 1904. Robert Abbe was the first, at least in America, to make interstitial application of radium into tumors (1905). Although Abbe is generally credited with being the father of interstitial radium therapy in the United States, Chase called attention to a letter from Alexander Graham Bell written in 1903 to the editor of *American Medicine* suggesting that, "There is no reason why a tiny fragment of radium sealed up in a fine glass tube should not be inserted into the very heart of a cancer, thus acting directly upon the diseased material." Abbe displayed enthusiasm in keeping up his special work in radium while at the same time continuing his surgical practice. He brought his first radium from Europe in 1903, using it to treat patients with carcinoma. He was largely responsible for collecting the $100,000 raised for the purchase of radium for Madame Curie when she came to America in 1921.

Chase compiled three lists, comprising 10 books, 112 original articles, and 17 editorials published in the United States prior to 1906 on radium and radioactivity. Most of the books had only a short chapter, varying from 5 to 50 pages, on the subject. The original articles appeared for the most part in medical journals, some in lay journals.

Robert Abbe's first article on radium (June, 1904) referred to observations he had been able to make during fifteen months with the "best radium made by the Laboratories of the Curies in Paris." He had used 15 cg. (2.25 grains), strength 300,000, meaning 300,000 times the strength of the radium in its original form in uranium.

Finzi, in discussing the evolution of radiation therapy, said that the clinical use of radium in England must have started in 1903, or perhaps a little earlier, since Radcliff Crocker described telangiectases from overdosage in 1902, and usually it takes a year or more after the irradiation for these reactions to appear. Finzi used interstitial radiation as early as 1909, by burying a 25 or 50 mg. tube. Joly and Stevenson of Dublin in 1910 introduced needles containing much smaller quantities of radium into growths. This technique was developed by Bayet in Brussels, Regaud in Paris, Cade, Harmer and others in England.

Janeway is credited with the popular use of glass seeds containing radon for interstitial use. As mentioned above, the employment of capillary glass tubes containing radon, and placed in hollow needles, for the purpose of interstitial treatment was first reported by Joly and Stevenson of Dublin. Duane was first to suggest the use of glass radon seeds discharged into a tumor and left there permanently, a method which was used to some extent at the Huntington Memorial Hospital by his clinical associates; but it was Janeway (1918) who really worked out the proper dosage (empirically) and used it very extensively for all types of cancer at the Memorial Hospital.

The glass radon seeds had the great disadvantage of producing intense necrosis in the immediate vicinity, because of the beta radiation which easily passed through the glass. It was for this reason that in the years 1924–1925 Failla developed the gold

radon seeds which at once found favor with the clinicians at the Memorial Hospital and completely replaced the glass seeds. This interstitial use of needles and gold radon seeds was put on a scientific basis by Douglas Quick, Quimby, Paterson and Parker, Wilson, and others. Charles Martin gave added impetus to popularization of the use of low intensity radium needles.

Since France was the birthplace both of radium and of radium therapy, let us devote more detailed attention to Paris. Danne made available the first few milligrams of radium for Dr. Wickham. Dominici is credited with the introduction of screens and filters in the clinical use of radium. It was learned very early that they had need for some improved material that could be moulded to the shape of the patient's face in order to support the radium sources at fixed distances from the skin. Alfonso Esguerra Gomez of Colombia, with Monod and Richards, was charged with the task of finding a suitable substance for this purpose; the result was a mixture of paraffin, beeswax and sawdust which Regaud named Colombia paste. As a matter of fact, Janeway in 1915 or 1916 had used for this same purpose a dental compound known as Kerr's wax for making moulds and imbedded in them filtered radon tubes. Colombia paste was intended to be an improvement on Kerr's wax and for many years served a very useful purpose all over the world; but with the diminishing favor of surface applications of radium, its employment has almost disappeared.

In December, 1909 the University of Paris proposed to the Pasteur Institute that inasmuch as Austria was at that very moment erecting a special institute for the study of radioactive substances, and since the University of Paris had not been able to provide for Madame Curie and her collaborators anything more than a very small laboratory located within another service, they join in the provision of an appropriate special laboratory for radium, to function with a double purpose: one part for research on the phenomena of radioactivity, to be directed by Madame Curie and her successors in the chair of physics created for Pierre Curie, and the other part (the Institut du Radium) dedicated to biologic and medical applications of radioactivity to be under the control of the Pasteur Institute. Professor Claude Regaud of Lyons was designated as Director of the Institute of Radium. The Institute was opened a few months before the outbreak of World War I, but no work was done from 1914 to 1918. During the war Regaud recruited Coutard, Lacassagne, Roux-Berger, Monod, and Pierquin, who constituted the nucleus of workers eventually developing the techniques of radium therapy as used at the Radium Institute. A number of our own Society members took a considerable part of their training there, including, T. Leucutia, Juan del Regato, Simeon Cantril, Maurice Lenz, Jacob Freid, Fernando Bloedorn, Will Harris, and perhaps others. I spent a few weeks there about 1921. William Duane spent about six years ending in 1913 as assistant to Pierre Curie and later to Madame Curie.

The use of radium in large quantities arranged in a single applicator apparently started with Finzi, who assembled over 600 mg. in 1911 for use on a millionaire patient. In 1914 Cameron prepared for a breast cancer a pack containing 1,020 mg. in tubes of varying amounts applied at a distance of 5.5 cm. from the skin, screened with 0.5 mm. silver and 1.0 mm. brass. Following this experience a radium surface pack was considered to mean 1 to 4 gm. of radium element (or equivalent in radon) divided into 50 or 100 mg. tubes, arranged in a somewhat regular form, usually circular, over a given area. About 1920, Lazarus-Barlow used 5 gm. for a year in experimental work. Forssell and Berven in Stockholm, Cutler in Chicago, and others have used packs or "bombs" of 5 to 10 gm. However, since the benefits of nuclear fission have been applied to radiotherapy, the small radium "bombs" are being displaced by much larger quantities of cobalt or cesium. Quick of New York works with

an especially designed radium applicator containing 50 gm.

Regaud was probably the first in Paris to use a large amount of radium for external radiation in serious clinical work. For several years in the late twenties and in the early thirties he employed 3 to 4 gm. of radium, convinced that radium had a more selective effect, and that, all other circumstances being the same, it should yield better results than less penetrating roentgen rays in the treatment of deep-seated cancers. He obtained also a loan of 14 gm. of radium, and about 1933 he started a special clinical project, with del Regato as his first assistant. They treated cervical carcinoma with a 10 gm. bomb and laryngeal carcinoma with 4 gm. But the radium could not be placed at a distance of more than 10 cm., and the source was almost as big as the field. As a result the irradiated volume was too large, systemic reactions too great, daily doses relatively small. After a while radium emanation was discovered in the air, and the department was closed until the leaking tubes could be sealed. It was concluded that the radium showed no important superiority over lesser potential roentgen therapy, which was more elastic and less dangerous to everyone concerned.

At the Radium Institute they never used seeds, but employed glass tubes containing emanation in hollow platinum needles for interstitial implantation. In spite of the name of the institution and the bias in favor of radium from the radiobiologic standpoint, it was here that roentgen therapy flourished greatly, especially through the work of Henri Coutard.

Regaud and Lacassagne used to bicycle to the big hospitals in Paris with a lead box containing the few milligrams of radium which they used in the early trials that began the long path that led to the techniques now universally adopted. Regaud usually had a return ride offered him by one of the professors, and Lacassagne bicycled back to the Institute of Radium pulling Regaud's bicycle by the hand to have it ready for their next expedition.

Space does not permit review of the details of other world-renowned radium institutes, the best known of which is perhaps the Radiumhemmet of Stockholm, founded in 1910 by John Berg, a surgeon. The little trial hospital Radiumhemmet of 1910 with only 16 beds, a single roentgen apparatus and 120 mg. of radium, under the far-sighted guidance of Gösta Forssell developed into King Gustav V's Jubilee Clinic of the Karolinska Sjukhuset with its three sections: Radiumhemmet, the Institute of Radiophysics, and the Institute of Radiopathology.

Similarly the Radium Institute of London from a modest beginning grew to great prominence. *The British Medical Journal* for March 5, 1904 mentioned that radium was used in the treatment of cancer in the Middlesex Hospital, the Cancer Hospital, and other metropolitan hospitals. A little over a month later, April 23, 1904, the same journal recorded that the Goldsmiths Company had placed the sum of one thousand pounds sterling at the disposal of the Council of the Royal Society for the purpose of investigating the properties of radium. The London Letter in the *Journal of the American Medical Association* (1910, *55*, 1658) mentioned that the London Radium Institute had contracted with the Austrian Ministry for 1 gm. of radium for $75,000. This purchase was made on behalf of Sir Ernest Cassell, who was to present it to the institution. The London Radium Institute was formally dedicated about 1911, with A. E. Hayward Pinch as Director. The Holt Radium Institute at Manchester was founded earlier (about 1905, according to Dr. Fricke). The Marie Curie Hospital in London, the Mount Vernon Hospital, and Westminster Hospital were only a few of the radium centers established in England. I will not attempt to go into any detail about them, except to say that, according to Dr. Lederman, large amounts of radium were acquired by the Middlesex Hospital in 1919. In 1929 Westminster Hospital had a 4 gm. pack, as did also the Cancer Hospital (now known as the Royal

Marsden Hospital). By 1935 the three hospitals just named, as well as the Radium Beam Research Institute, were functioning as well-equipped radium centers.

In the United States, the Huntington Hospital of Boston, with Professor Duane, began its very early work with radium about 1913, a natural consequence of the six years which Professor Duane had spent with the Curies in Paris. After his return to Harvard, with the radium at his command he worked for a number of years in the Huntington Hospital and in other clinics, not only as a physicist but in the application of the radium to patients.

As already stated, Dr. Howard Kelly by 1914 had acquired a considerable amount of radium, 1 gm. or more, and in 1917 as much as 5 gm. About the same amount was in the possession of the Memorial Hospital in New York. Some details regarding the early radium work at the Memorial Center for Cancer and Allied Diseases in New York should be recorded. About 1913, this institution, then known as the General Memorial Hospital and receiving all kinds of cases, began to specialize in the treatment of cancer. Also about that time Dr. James Ewing became associated with it and served as Director until 1939. Some radium was acquired about 1914, at which time a radon plant was installed. The amount of radium at the Memorial Hospital increased steadily through gifts by Dr. James Douglas until it amounted to 4 gm. in 1917, all of it in solution, radon being used for all treatments. It is probable that the first radon plant in this country was installed and operated by Howard Kelly with the aid of an assistant sent from Rutherford's laboratory. By 1917 Doctor Kelly had 5 gm. of radium, all in solution in the radon plant. The Memorial Hospital radon plant was of the type developed by Debierne and Duane in the laboratory of Madame Curie in Paris. Failla, who began work at the Memorial Hospital in December, 1915, worked constantly to improve the radon plant and ultimately had it mounted on a solid steel frame; he also made its operation semiautomatic, thus very greatly reducing the radiation exposure incurred in the collection process. Something like thirty of these instruments were installed in the United States and other countries. The experience of Duane, Ewing, Janeway, Failla, Kelly, Burnam, Henry Schmitz, and others in the United States, in conjuction with the information communicated from European radium centers, had set up a reliable pattern for the practice of radium therapy on a reasonably sound basis. Ewing and Janeway with the advice of Professor Duane and the phenomenal development of the principles of radium dosage by Failla and Quimby, Paterson and Parker and their colleagues in Manchester, and others have brought the practice of radium therapy to a high plane of scientific accuracy, not only for radium alone but for the combination of radium and roentgen rays.

* * *

On October 26, 1916 the American Radium Society was formally organized at the Rittenhouse Hotel in Philadelphia. There had been a preliminary conference during the American Medical Association meeting of June, 1916 in Detroit. C. H. Viol, Ph.D. and W. H. Cameron, M.D. of Pittsburgh, associated with the Radium Chemical Company, were very active in the preliminary arrangements. At the first formal meeting on October 26, 1916, a constitution was adopted by unanimous vote, and the chairman of the Organization Committee, W. H. Cameron, announced that there were nineteen active members and one associate member. The names are not included in the original record, but based on a very careful review of the subsequent records, I am certain that the founding members were as follows: Robert Abbe, New York, New York; W. H. B. Aikins, Toronto, Ontario, Canada; C. E. Alliaume, Utica, New York; Joseph B. Bissell, New York, New York; R. H. Boggs, Pittsburgh, Pennsylvania; W. H. Cameron, Pittsburgh, Pennsylvania; James T. Case, Battle Creek, Michigan; Howard Fox, New York, New York; S. C. Glidden, Danville,

Illinois; T. C. Kennedy, Indianapolis, Indiana; J. M. Lee, Rochester, New York; Isaac Levin, New York, New York; H. W. Longyear, Detroit, Michigan;R. E. Loucks, Detroit, Michigan; H. K. Pancoast, Philadelphia, Pennsylvania; D. T. Quigley, Omaha, Nebraska; M. M. Rosenthal, Fort Wayne, Indiana; Henry Schmitz, Chicago, Illinois; Frank E. Simpson, Chicago, Illinois; and C. H. Viol, Pittsburgh, Pennsylvania (associate member).

Of these, D. T. Quigley and your speaker are living today. Aikins was president; Boggs, vice-president; Pancoast, corresponding secretary; and Loucks, recording secretary and treasurer. Apparently the only scientific contribution was by C. H. Viol, a physicist, presumably on the physical aspects of radium therapy.

Doctor Aikins, always a progressive physician in the forefront of the advance of medicine, was one of the first to study treatment by the use of radium and he had a large quantity of radium at his command. He followed very closely the early work of Wickham of Paris and of Robert Abbe and Howard Kelly in this country.

Russell H. Boggs was an important early roentgenologist. About 1911 he first worked with mesothorium instead of radium, and later, on this account, was jokingly told he did not belong in the radium society. His treatments were often supplemented with roentgen rays. Between 1903 and the time of his death, he contributed 35 articles on the subject of radiology, about one third dealing with mesothorium and with radium, a supply of which he obtained in 1915. He treated some cases of cancer by imbedding radium, supplementing the dose with roentgen rays.

Pancoast was the first professor of radiology in the Medical School at the University of Pennsylvania and very active in the American Roentgen Ray Society, of which he was president in 1913, and president of the American Congress of Radiology of 1933. His major interest was in roentgenology. He was especially interested in safety for radiologist and patient.

The contributions to radiology by Loucks of Detroit dealt particularly with the radium therapy of thyrotoxicosis.

Doctor Viol was an exceptionally brilliant physicist and gave many years of his life in the development of radium for therapeutic purposes. Among his outstanding accomplishments were the production of radium salts of high purity; and the development and definition of the physics of radioactivity to the great advantage of radium therapists. He continued his work with radium even after he recognized that this radioactive substance was the cause of his terminal illness.

The second meeting took place in New York, June 4, 1917, with fifteen members present, and Doctor Aikins presiding. Several of us were already in military service. A large number of new members were elected, including: Curtis F. Burnam, Baltimore, Maryland; Walter B. Chase, New York, New York; John G. Clark, Philadelphia, Pennsylvania; James A. Corscaden, New York, New York; C. E. Field, New York, New York; H. H. Janeway of the Memorial Hospital, New York, New York; Douglas Moriarta, Saratoga, New York; W. S. Newcomet, Philadelphia, Pennsylvania; E. C. Samuel, New Orleans, Louisiana; Albert Soiland, Los Angeles, California; and several others, twenty-five in all. Four papers were presented, including discussions of the physics of radium for the radiologists, radium in general surgical practice, methods of treating the lower urinary tract, histologic findings in tissues treated by radium (H. Schmitz), and case reports.

The third annual meeting occurred at the Palmer House, Chicago, June 10, 1918, with John M. Lee presiding, with only sixteen members present, military duties accounting for the absence of a number (including myself). Robert Abbe was elevated to honorary membership, but he said he preferred to remain active, so the motion electing him was amended to read "active honorary member." The balance in the Society's funds was $114.80. This meeting

marked the first participation of James Ewing in the program of the Society, an association that was to prove so valuable in the ensuing years. New members elected included Leda Stacy of the Mayo Clinic, Rochester, Minnesota; W. L. Clark, Philadelphia, Pennsylvania; and Gioacchino Failla of the Memorial Hospital, New York, New York. Papers were listed on the use of radium in gynecology (T. J. Watkins and Leda Stacy) and others on radiation physics and radium in general practice. At this meeting the Society voted to publish its Proceedings in the American Journal of Roentgenology. At the meeting of the American Roentgen Ray Society at Saratoga in 1919, it was on my motion that the Society added the words "and Radium Therapy," giving its Journal the name American Journal of Roentgenology and Radium Therapy.

The fourth meeting took place in Atlantic City, June 9, 1919, under the chairmanship of Henry Schmitz, Chicago, (in the absence of the president, F. E. Simpson, who was ill). Seventeen members and thirty-three guests were present. The treasurer closed the year with $130.70. This scientific meeting included papers by Pfahler, on the combination of radium, x-rays and electrocoagulation with surgery in the treatment of malignant disease; by Soiland on the comparative action of radium and x-rays, and a paper on the treatment of arthritis with radium (apparently by oral administration). New members included Gerber, Kirkendahl, Pfahler, Quick, Skinner, Rollin Stevens, and others. This was the first year, I believe, in which qualifications for membership were formalized. Applicants were required to state data regarding graduation, amount of radium in possession, and to include a report of 25 cases treated. A research committee was appointed for the purpose of standardizing records and reporting radium treatments. Janeway reported on deeply implanted radium emanation tubes.

The fifth annual meeting was held in New Orleans, April 20, 1920, with Henry K. Pancoast presiding. The scientific papers had relation chiefly to gynecologic applications of radium, including a report by Stacy of 600 cases of menorrhagia and uterine myoma. C. Jeff Miller of New Orleans, Skinner and Schmitz also took part in this gynecologic symposium. Other contributions included angiomas treated by radium, and Janeway had another paper on the use of emanation. G. E. Pfahler talked on cancer of the breast. J. M. Martin of Dallas presented a movie of his work with early and late carcinoma treated with radiotherapy, for which he was given a special vote of thanks.

At the sixth annual meeting in Boston in 1921, under the presidency of Henry Schmitz, the guests of honor were Elis Berven of Stockholm and W. D. Coolidge. The annual dues were increased to $12.00 to include subscription to the American Journal of Roentgenology and Radium Therapy, the official organ of our Society. The death of Henry H. Janeway, head of the radium department of the Memorial Hospital, New York, dampened the spirits of this meeting.

The seventh meeting in 1922, under the presidency of George E. Pfahler, was noted for the effort made to secure a ruling by the Internal Revenue Department that the purchase price of radium for therapeutic purpose be declared deductible as expense, provided that in the event of sale of the radium the amount received be recorded as income. You all know that this effort was in vain. William Duane, W. D. Coolidge, and Claude Regaud were elected honorary members at this meeting.

The eighth annual meeting, 1923, was held in San Francisco, with Lars Edling of Lund as the distinguished guest.

The ninth annual meeting, 1924, was held in Chicago, under the presidency of your speaker. Four distinguished scientists were elected honorary members, including James Ewing, Gösta Forssell, Ernest Rutherford, and A. E. Hayward Pinch of London. Robert Abbe, Madame Curie, Howard A. Kelly, and Francis H. Williams had already been made honorary members. It was a matter of particular pride that I had been

able to arrange for the presence of Claude Regaud, of the Institut du Radium, Paris. His address was the great event of the meeting.

On this visit Professor Regaud had been breakfasted and lunched and dined by various medical organizations, radiological and otherwise, in New York, Philadelphia, Washington, and other centers, including Chicago, so that he had had very little time for himself. After returning home he wrote me a letter, recognizing my good offices in arranging his American visit and thanking me profusely for the "wonderful but terrible American hospitality," with which he had been entertained, and inviting our members to visit the Radium Institute of the University of Paris.

I have in my files notes about each of the annual meetings up to and including 1934. We had had up to that time fifteen honorary members: Robert Abbe, New York, 1918; Marie Curie, Paris, 1921; Howard A. Kelly, Baltimore, and Francis H. Williams, Boston, in 1921. In 1922, William Duane of Boston, William D. Coolidge of Schenectady and Claude Regaud of Paris were added to the list; in 1924 James Ewing, New York, Gösta Forssell, Stockholm, Sir Ernest Rutherford, and A. E. Hayward Pinch of London. In 1931 Francis Carter Wood of New York, Carlos Heuser of Buenos Aires and Pedro Castro Escalado of Buenos Aires were elected honorary members, and in 1932 Dr. N. Ernest Dorsey of Washington, D. C., who was largely responsible for the formation of the National Bureau of Standards.

I terminated my review of our records with the year 1934. I would like to suggest that future annual booklets of the Society should contain the list of all who have been or are honorary members, marking the deceased ones with a star or small cross in front of their names. Of the fifteen just mentioned elected up to and including 1932, twelve have gone to their reward, the only living ones of the group being William D. Coolidge, Pedro Escalado, and N. Ernest Dorsey. The names of all these scientists greatly honor our Society and we should do well to keep them on the list of honorary members.

We have not time here to go further into the early history of the American Radium Society. Our records are excellent except for the first two or three meetings. They comprise wonderful contributions, including numerous symposiums on the physics and biologic effects of radium; dosage calculations and standards; groups of communications on gynecologic applications of radium; discussions of combined radium and roentgen techniques; irradiation of malignant lesions of the head, neck, breast, bladder, prostate, and ovarian regions; in short, every problem associated with radium and its therapeutic applications has been presented, usually more than once. The printed record in our official organ forms a valuable source material. An imposing list of outstanding physicists, physiologists and physicians have participated in our programs and many of them have joined our ranks from time to time. Our speakers, as listed on the program from year to year, constitute an impressive array of scientific talent. It is impossible on this occasion to name them and comment on their special qualifications, but in closing I cannot fail to express our gratitude to our physicists for their long and faithful service to our Society, especially Drs. Failla and Quimby, who have done so much to set up the standards and methods of dosage measurement which constitute the very basis of successful radium practice. They have given freely of their knowledge in the instruction of a host of us, members of this Society and many others.

2315 Bath Street
Santa Barbara, California

The writer wishes to express sincere thanks for aid in preparing these remarks to Drs. Juan A. del Regato, Gioacchino Failla, Robert E. Fricke, George W. Grier, Douglas Quick, Robert MacKenzie, Mather Cleveland, Richard B. Stark, A. Lacassagne, and to Mrs. George E. Pfahler.

PRESENTATION OF THE JANEWAY MEDAL

By MILFORD D. SCHULZ, PRESIDENT

Ladies and Gentlemen:

We now come to that part of our program given to honoring those who have contributed in outstanding measure to our understanding of ionizing radiation and its therapeutic use in medicine or to those many problems, physical, biologic, medical, educational, or economic with which its use is in some way ancillary.

The Janeway Medal is this Society's highest mark of recognition. In the course of the years twenty-three such medals have been struck and bestowed upon a select group of physicians and scientists to whom we of this Society owe so much. Tonight this number becomes an even two dozen.

Our new medalist is a man of many parts and unusual talents. He may look to many of you just like anyone else, a little more plump perhaps, but he isn't. He is a phenomenon of nature. Where many people would have been willing to rest on past achievements, Dr. Case defies the words of the prophet. Desire—for knowledge at least—has not failed, nor has the grasshopper become a burden.

Dr. James T. Case, eminent physician, teacher, scientist, and author; and, if I may sneak my own kudo in here, my medical sire, I take especial pride in welcoming you to the distinguished company of Janeway medalists, and, in recognition of your outstanding achievements and contributions to medicine, ask you to accept this token of the American Radium Society's regard. I am sorry Mrs. Case could not be here, for I should like to have given half of this medal to her for I know that it is hers.

THE PHYSICAL ASPECTS OF A CESIUM TELETHERAPY SOURCE*

By CHARLES S. SIMONS, PH.D., ISADORE LAMPE, M.D., *and* HOWARD B. LATOURETTE, M.D.†
ANN ARBOR, MICHIGAN

A 2,000 curie teletherapy source of cesium barium 137 has been loaded into an A.E.C.L. Model B Theratron for an evaluation program at the University of Michigan Medical Center. The investigative work has been performed at the request of and under the sponsorship of the United States Atomic Energy Commission. Because of certain aspects of the cesium source, several modifications of the theratron were required. A discussion of the physical qualities of the source, the theratron modifications and some data on ionization distribution in a water phantom follows.

THE SOURCE DESIGN

The design of the source was dictated by the method of preparation of the CsCl precipitate from gross fission products, by the large amount of self-absorption of the gamma rays in the source, by the source drawer size in the theratron head, by the low specific activity of the source material, by the relation of penumbra to the diameter of the source, and by the cost of the source at the time it was ordered (the price has been reduced markedly recently).

Several criteria were set up for a satisfactory source: (1) the output should be at least 30 r/min. at the treatment distance, which is approximately 75 cm. for the theratron; (2) the source diameter should be of the order of 2 cm. in order that the penumbra be moderate; (3) it would be desirable for the source to fit into the international source capsule.

For a cesium source to have an output of 30 r/min. at 73.8 cm. source skin distance (SSD, the distance from the bottom of the source to the axis of rotation), it must have an effective strength of 2,620 curies. The minimum diameter that can present such an effective strength is 3.34 cm., but such a source would have to be of infinite thickness. Obviously, if the desired output at the axis of rotation were to be obtained, a larger source diameter would be required, making the penumbra problem more severe. Since the international source capsule will not hold a source of larger diameter than about 2.85 cm., the third criterion could not be achieved either. Accordingly, the source was designed as a compromise. Its diameter of 1.25 inches (3.184 cm.) was chosen as it is the size of a certain standard stainless steel filter disk in use at Oak Ridge National Laboratory where the source was prepared. A design figure of 2,000 curies was selected, giving a source height of 3.66 cm. The source, when prepared, was assayed at 2,045 curies and its three cesium chloride disks had a total thickness (source height) of 3.75 cm. The effective source strength, calculated by the method of Dixon,[2] using a value of 0.23 $cm.^{-1}$ for the absorption coefficient,[1] was computed to be 1,370 curies.

The output, which will be discussed later, was approximately 8 r/min. at one meter or 14.6 r/min. at the axis of rotation. One reason for the low output is that the specific activity of the cesium source is only 22.4 curies/gram. This value seems at first glance to be very low for a source prepared from gross fission products and one is tempted to ask if the specific activity could not be made considerably larger. For an answer one needs only to compute the maximum specific activity of carrier-free

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cesium metal. Using a half-life value of thirty years, it is computed to be 79 c/g. Since the source is cesium chloride, the maximum specific activity in terms of the cesium is reduced to 63.1 c/g. In the preparation of the source a certain amount of stable cesium is added as a carrier to bring about the precipitation of cesium from the mixed fission products solution. If this were to be an amount equal to the quantity of active cesium to be precipitated, the resulting specific activity would be halved or 31.5 c/g. A final step in the preparation involves drying the precipitate and compressing the powder in a mechanical press. The density[4] of crystalline CsCl is 3.97 g/cm.^{3}, but the density of our cesium source was only 3.05 g/cm.^{3}. Consequently, the value of 31.5 c/g, reduced in the ratio of 3.05/3.97, gives a resulting specific activity of 24 c/g (compared to the actual specific activity of 22.4 c/g of our source).

THE SOURCE CAPSULE

The source capsule was made from #316 stainless steel in the form of two sealed containers, one nesting inside the other, each having silver solder seals. The bottom ends of the inner and outer containers have each a thickness of 0.020 inches. The combined thicknesses present an attenuation factor of 0.944 to the output of the source. The dimensions of the source and outer capsule are shown in Figure 1. The outer container in turn (Fig. 2) fits into the theratron source liner which had to be modified by boring its top section to take the assembly, which is 0.630 inches longer than the international capsule. The outside diameter of the assembly was made only one-half millimeter larger than that of the international capsule in order to reduce the motion of the source holder in the source liner during rotation of the theratron head. Our previous experience with a cobalt teletherapy source in a theratron showed that 1 mm. of sideways motion of the source results in a 3 mm. shift of the radiation field with respect to the light localizer field.

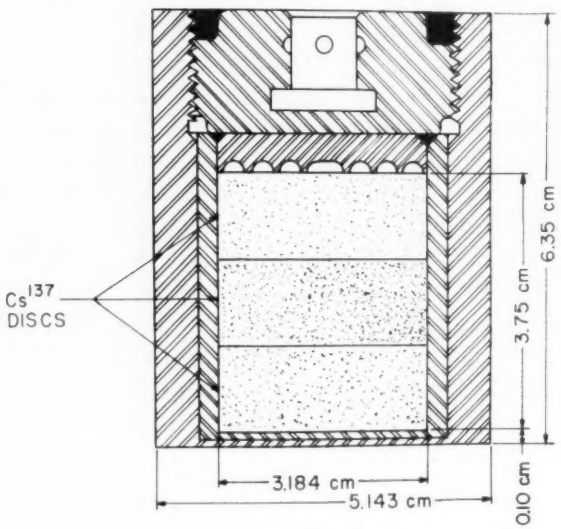

Fig. 1. Assembly drawing of cesium 137 source and double sealed source capsule.

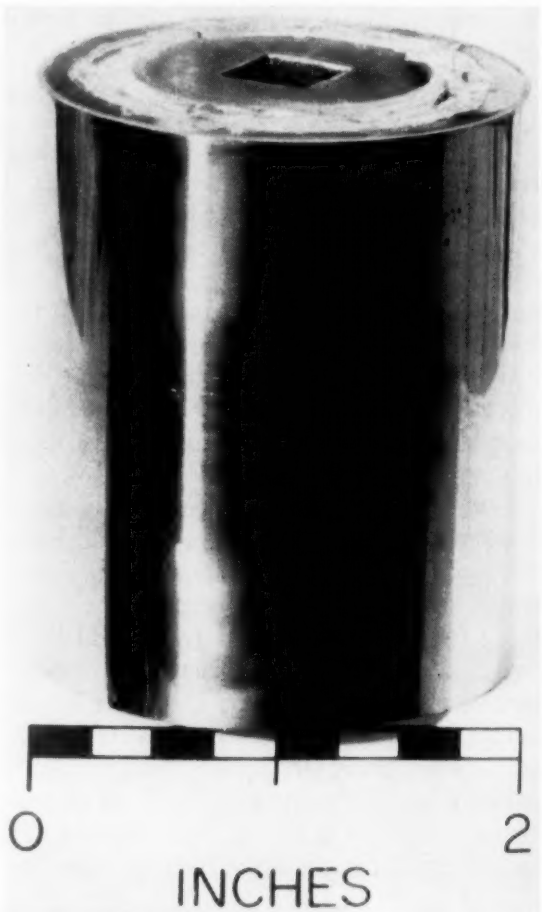

Fig. 2. Photograph of completed cesium 137 teletherapy source capsule. (Courtesy J. H. Gillette, Oak Ridge National Laboratory.)

MODIFICATIONS OF THE THERATRON TO COMPENSATE FOR THE LOW SOURCE OUTPUT

The low exposure dose rate of 14.6 r/min. at the axis of rotation of the theratron was unacceptable on the basis of the length of time which would be required for treatment of each patient. It was decided to change the SSD from 73.8 cm. to 50 cm. This change produced the following consequences: (1) The output was raised to 31.8 r/min. for a 10×10 cm. field which is comparable to the exposure dose rate from a 220 kv. peak, Villard type roentgen ray unit operating at 20 ma. with a Thoraeus I filter and the same target skin distance; (2) there was a small decrease in percentage depth dose due to the reduction in SSD; (3) rotational therapy could not be employed; and (4) the field sizes were limited to 10×10 cm.

Since consequence (1), the dose rate improvement, was a major item and consequences (2) and (3) were minor, the diaphragm system was examined to see if larger field sizes could be made available by a modification of the diaphragm. In the following three paragraphs the several modifications to the theratron are described.

A. Table Modification. To enable the table to raise the patient close enough to the source, a permanent extension was added to the column that supports the table. This consisted of a 6 inch length of 8 inch extra-heavy steel pipe which was bolted to the top end of the column. When the theratron head is rotated into a position to treat the patient through the underside of the table, the extension is of the proper length to permit the table to be lowered to the 50 cm. source skin (tabletop in this case) distance.

B. Diaphragm Modification. The theratron adjustable diaphragm was designed by its manufacturer to have a maximum field size of 15×15 cm. at a 75 cm. source skin distance. In order to use a 50 cm. source skin distance, either a maximum field size of 10×10 cm. at this distance must be accepted, or a change must be made in the diaphragm. The modification amounted to removing a small amount of the outer end of each of the 4 tungsten blocks (Fig. 3) so that the blocks could be moved further apart without hitting the outer wall of their container. The holes in the two rotating plates that are used to adjust the diaphragm-block spacing were turned out to a larger inside diameter and the 4 ball bearings were relocated at a larger radius. With the above modification the maximum field size has been increased to 13×13 cm. at 50 cm. SSD or 20×20 cm. at 75 cm. SSD.

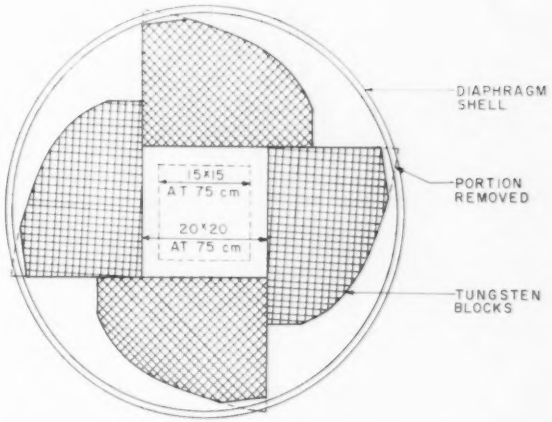

FIG. 3. Schematic drawing to show the modification of the tungsten adjustable diaphragm blocks to increase the maximum field size by 33 per cent.

C. Light Localizer Modification. With the increased field size available, it was found that the mirror system for the light field localizer did not reflect the light to the edge of the radiation field for the large field sizes. The modification to the light system was in essence the replacement of the mirrors (Fig. 4) with new ones of larger size to give greater field coverage. The construction of new mirror holders had to be kept to angular tolerances of ±2 minutes of arc and the flatness of the aluminized mirrors had to be held to less than 20 rings of sodium light. The isodose plotter was used to adjust the light field so that the dose rate at the edges of the field was 50 per cent of the dose rate at the center of the field.

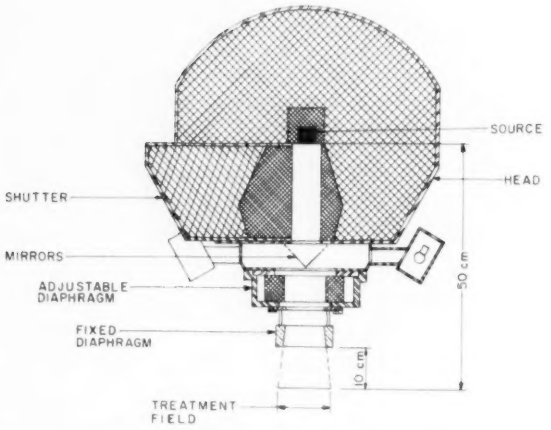

FIG. 4. Schematic drawing to show the location of the fixed diaphragm and the increased size of the mirrors (dotted lines).

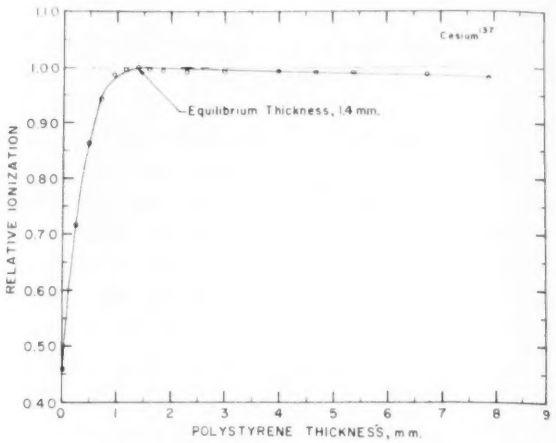

FIG. 5. Build-up in ionization measured in an extrapolation chamber as a function of wall thickness.

SOURCE CALIBRATION

In order to measure the exposure dose rate, one must ascertain the thickness of ionization chamber wall necessary to produce electronic equilibrium. For this purpose several polystyrene caps were made, having as their inside diameter the outside diameter of the thimble chamber of a calibrated Baldwin-Farmer substandard dosimeter and having wall thicknesses ranging from 0.3 to 5.5 mm. The caps were successively placed on the thimble chamber and exposed for the same length of time to the cesium gamma ray beam. When the readings of the Baldwin-Farmer instrument were plotted as dose rate versus total thickness of cap and thimble, the maximum dose rate was found to occur at 1.4 mm. total thickness. This value for the equilibrium thickness was verified by building a parallel plate chamber of polystyrene having a Saran upper electrode, rendered conductive by a coating of Aquadag. The thickness of the Saran sheet was 0.02 mm. Successive layers, 0.25 mm. each, of "high-impact strength" polystyrene, specific gravity 1.00, were placed on top of the upper electrode. A plot of relative ionization versus polystyrene thickness is shown in Figure 5. The maximum value, 1.4 mm., is taken to be the location of the maximum dose rate in tissue irradiated by cesium gamma rays. In the same figure it can be seen that the surface dose is 46 per cent of the maximum dose. One inference from the proximity of the epidermis to the point of maximum dose is that more skin reaction should be anticipated with cesium than would be seen with cobalt gamma ray treatments. The maximum dose rate for cobalt occurs at about 5 mm. below the skin surface.

A second flat ionization chamber (Fig. 6) was designed somewhat after Trump and Cloud.[7] The chamber was made from

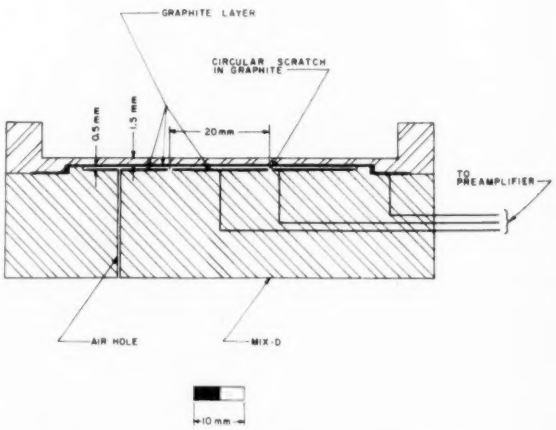

FIG. 6. Schematic drawing of parallel plate chamber made from Mix-D, having an equilibrium thickness wall used for the measurement of absorbed dose rates.

Mix-D, having an upper wall thickness of 1.5 mm. and an air space 0.5 mm. thick. The lower collecting electrode was 2 cm. in diameter, surrounded by a guard ring having a 6 cm. outside diameter. The inner surfaces were made conductive by spraying a thin, uniform coating of Aquadag from an artist's air brush. The ionization currents were measured with a modification of the DC amplifier described by Fedoruk, Johns and Watson[3] feeding a Brown Electronik Recorder. The chamber was designed also to fit into the center of three layers of Mix-D, each 30 cm. square by 1.2 cm. thick. With the addition of other layers of Mix-D above and below the chamber, readings were obtained from the chamber buried in various depths of "tissue."

In order to calibrate the flat chamber, a Victoreen "high energy" chamber was buried in other sheets of Mix-D at the several same depths as the flat chamber. The thimble chamber was exposed for known intervals of time in order to determine the dose rate at each depth. The Victoreen chamber had been calibrated with Co^{60} and 2 mm. Cu half-value layer radiations by the National Bureau of Standards. Since both the flat chamber and the thimble chamber were exposed to the cesium radiation at depths greater than the equilibrium thickness, it did not matter that the two chambers had greatly different wall thicknesses. The ratio of the dose rate measured by the Victoreen chamber to the reading of the flat chamber established a calibration factor for the flat chamber.

The exposure dose rates for the cesium source at 50 cm. SSD are given in Table I for the various field sizes utilized in treatment. These air dose rates were measured using a Victoreen 25 r chamber with a close fitting lucite cap which had a wall thickness of 0.88 mm. The thimble chamber wall thickness of 0.58 mm. plus that of the cap produced an equilibrium thickness of 1.46 mm.

The absorbed dose rates for the cesium source at 50 cm. SSD were measured with the calibrated Mix-D chamber. These values, measured in roentgens, were calculated in units of rads by multiplying them by the factor 0.966 rad/roentgen[5] and are listed in Table II.

Table I

CESIUM 137
EXPOSURE DOSE RATE
50 cm. source skin distance, 10 cm. diaphragm skin distance, July, 1958

Field Size cm.	Dose Rate r/min.	Field Size cm.	Dose Rate r/min.	Field Size cm.	Dose Rate r/min
4× 4	31.76	12×12	32.24	8× 7	32.69
5× 5	32.24	13×13	31.97	10× 8	32.69
6× 6	32.48	5× 4	32.00	11× 6	32.55
7× 7	32.65	6× 4	32.14	11× 7	32.62
8× 8	32.72	6× 5	32.34	12× 8	32.55
9× 9	32.72	7× 6	32.55	12×10	32.48
10×10	32.65	8× 6	32.62	13× 8	32.48
11×11	32.48				

ISODOSE CURVES

Since the extent of the penumbra is directly proportional to the source diameter, it was anticipated that due to the large diameter source there would be need for additional collimation required beyond that obtainable with the adjustable diaphragm of the theratron. Isodose curves for a 4×4 cm. field were first plotted using the adjustable diaphragm only. Next, with

Table II

CESIUM 137
ABSORBED DOSE RATE
50 cm. source skin distance, 10 cm. diaphragm skin distance, July, 1958

Field Size cm.	Dose Rate rad/min.	Field Size cm.	Dose Rate rad/min.	Field Size cm.	Dose Rate rad/min.
4× 4	29.87	12×12	31.90	8× 7	31.79
5× 5	30.72	13×13	31.79	10× 8	31.87
6× 6	31.15	5× 4	30.00	11× 6	31.51
7× 7	31.62	6× 4	30.44	11× 7	31.79
8× 8	31.90	6× 5	31.01	12× 8	31.94
9× 9	32.15	7× 6	31.29	12×10	32.15
10×10	32.12	8× 6	31.58	13× 8	31.65
11×11	32.15				

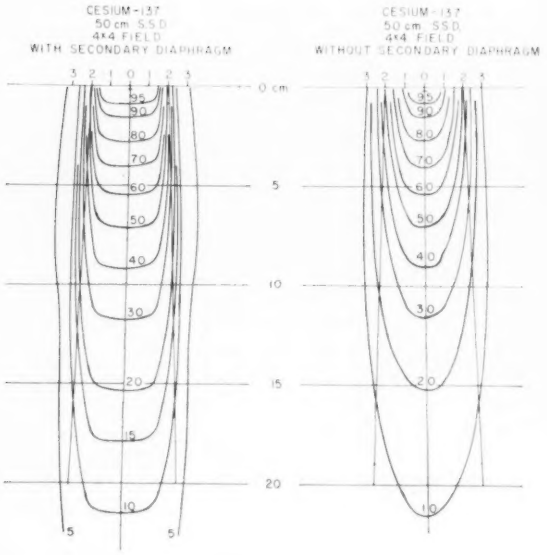

FIG. 7. Cesium 137 isodose curves for 4×4 cm. field with and without a secondary diaphragm.

4 lead bars one inch square in cross-section at the edges of the field, a secondary diaphragm was formed, having the bottom side of the bars placed at 10 cm. above the water phantom surface. Figure 7 shows the 4×4 cm. field isodose curves plotted with and without the secondary diaphragm in place.

Comparison of these 2 sets of curves shows the obvious advantage of the secondary diaphragms. An adjustable secondary diaphragm of lead was designed and constructed but it had to be abandoned because its required over-all dimensions interfered with the proper positioning of the patient's shoulders when a neck lesion was to be treated. A set of 22 fixed-field secondary diaphragms was constructed out of brass instead of lead. The decision to substitute brass included such points as ease in machining, greater resistance to distortion of the surfaces in general use, and reduced electron contamination by the use of a middle Z material. Figure 8 shows the theratron with one diaphragm in place and with several diaphragms placed inverted on the treatment table. The distance from the bottom of the diaphragm to the treatment surface is 10 cm. Each piece of brass is 2.5

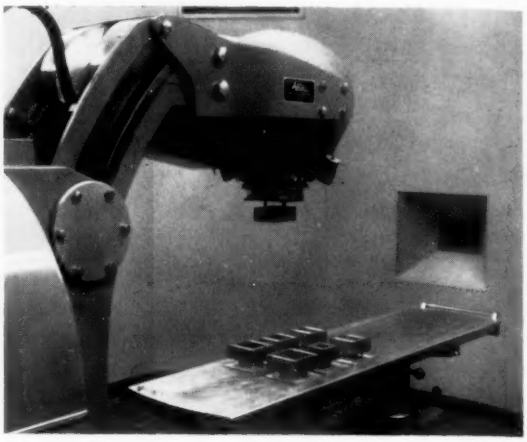

FIG. 8. Photograph of the theratron with one secondary diaphragm in place and 6 other diaphragms (inverted) on the treatment table.

cm. wide at its top and is 5 cm. deep. The inner surface is inclined at such an angle (different for each field size) that, if it were extended upward to the source, it would intersect the bottom area of the source at the center.

COMPARISON OF CESIUM 137 AND COBALT 60 ISODOSE CURVES

In comparing isodose curves for two energies of radiation, one should try to have identical source skin distances, diaphragm skin distances and field sizes. However, from the standpoint that one is forced to treat with shorter source skin distances with cesium than with cobalt due to the low specific activity of the former, the following comparison will be based on a 50 cm. SSD for cesium and a 73.3 cm. SSD for cobalt. Although isodose curves for cobalt could have been prepared for 50 cm. SSD, such comparison would be more of academic than practical interest, since most clinical workers would wish to extract the maximal potential from any teletherapy source that is used.

It can be seen for the 4×4 cm. field (Fig. 9) that the shape of the 2 sets of curves is almost identical, but that the depth dose at 10 cm. depth is one-third greater for the cobalt than for the cesium. For the 10×10 cm. field (Fig. 10) the curves are more

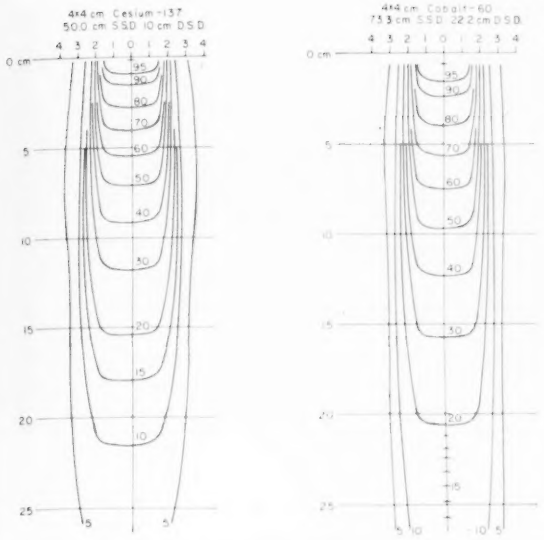

FIG. 9. Isodose curves for cesium 137 and cobalt 60: 4×4 cm. field.

rounded at the sides for the cesium, and the central depth dose at 10 cm. is one-fourth greater for the cobalt. For the 13×13 cm. field (Fig. 11) the width of useful field for cesium at 10 cm. is not much greater than for the 10×10 cm. cesium curve, as indicated by the decided rounding of the curves at the sides. The central depth dose at 10 cm. is for the cobalt again about one-fourth greater than that for the cesium. In Table III is listed the ratio of the central axis depth dose for cobalt 60 to that for cesium 137 for certain field sizes and depths in a water phantom.

TABLE III

RATIO OF CENTRAL AXIS DEPTH DOSES FOR SELECTED FIELD SIZES AND DEPTHS

Depth cm.	Cobalt at 73.3 cm. source skin distance / Cesium at 50.0 cm. source skin distance		
	Field Size		
	4×4 cm.	10×10 cm.	13×13 cm.
5	1.1	1.1	1.1
10	1.3	1.2	1.2
15	1.5	1.4	1.4
20	1.8	1.5	1.5
25	2.0	1.8	1.7

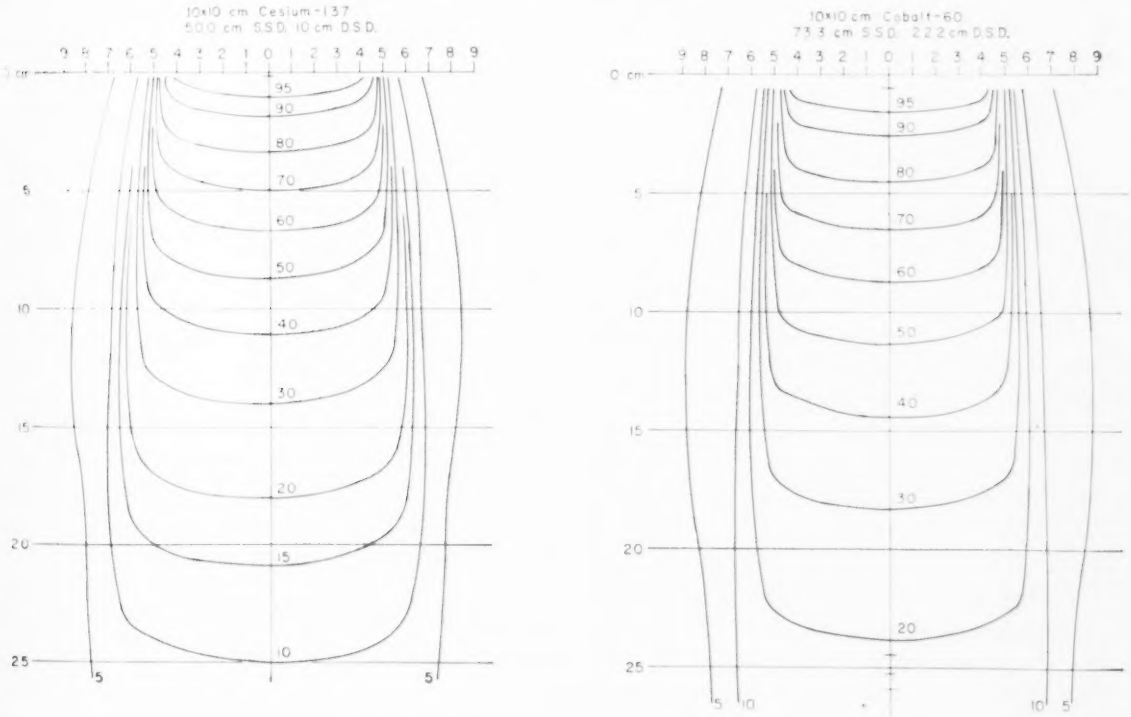

FIG. 10. Isodose curves for cesium 137 and cobalt 60: 10×10 cm. field.

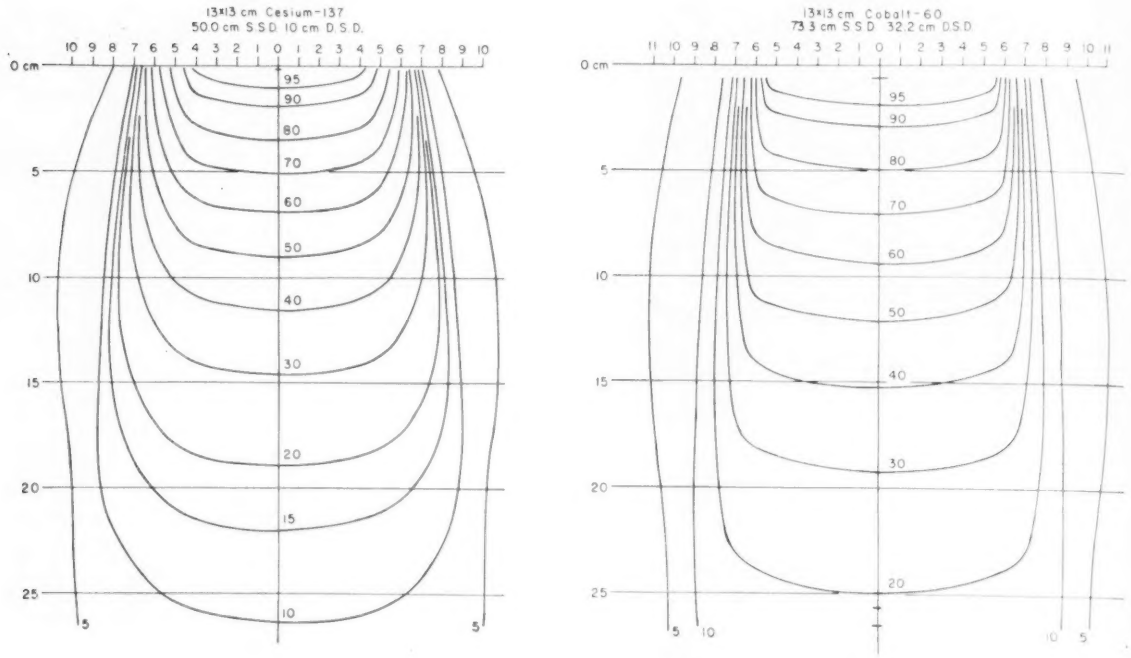

FIG. 11. Isodose curves for cesium 137 and cobalt 60: 13×13 cm. field.

DEPTH DOSE

Table IV gives the percentage depth dose values for square fields as a function of field area. In Figure 12 are plotted the family of curves relating depth dose to field size for the square fields using the secondary diaphragms. The data for Table IV and for these curves were obtained from central axis percentage depth dose curves. The latter curves, as shown in Figure 13, were obtained using our automatic isodose plotter[6] with the probe output adjusted to read 100 per cent at a depth of 0.15 cm. for each field size. The values of depth dose for the zero field size were computed by the following equation:

$$\frac{I_x}{I_0} = e^{-\mu(x-0.15)} \cdot \frac{(50.15)^2}{(50+x)^2} \cdot (100)$$

where I_x/I_0 = percentage depth dose at the depth x cm. in a water phantom the surface of which is 50.0 cm. from the source; $\mu = 0.083$ cm.$^{-1}$.

Table V lists the values of the linear absorption coefficient and half-value layer for several substances obtained under conditions of broad beam geometry.

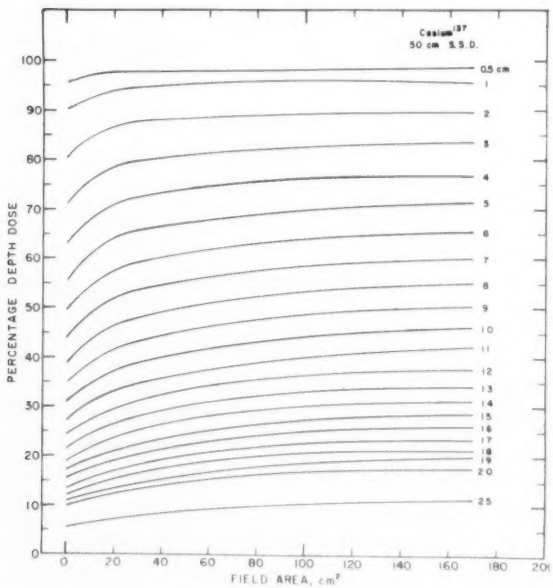

FIG. 12. Family of curves for cesium 137 relating percentage depth dose as a function of field area for various depths in a water phantom.

SUMMARY

1. A 2,000 curies cesium 137 teletherapy source has been designed for use in a theratron.

TABLE IV

DEPTH DOSE DATA FOR CESIUM 137 GAMMA RAYS
50 CM. SOURCE SKIN DISTANCE, 10 CM. DIAPHRAGM SKIN DISTANCE

Depth cm.	Area cm.²					
	0	25	50	75	100	150
0.15	100.0	100.0	100.0	100.0	100.0	100.0
0.50	95.8	98.0	98.2	98.4	98.8	98.6
1	90.1	94.4	95.2	95.6	96.0	95.7
2	80.2	87.0	88.0	88.4	88.8	89.6
3	70.6	79.6	81.2	81.8	82.4	83.3
4	62.6	72.0	74.2	75.3	76.0	76.8
5	55.5	65.2	67.6	68.5	70.0	71.0
6	49.3	58.4	61.4	62.5	64.0	65.3
7	43.9	52.8	55.6	57.0	58.4	59.8
8	38.9	47.4	50.4	51.9	53.4	54.8
9	34.7	42.8	45.3	47.3	48.6	50.2
10	30.8	38.4	41.2	42.8	44.4	46.1
11	27.5	34.4	37.2	38.7	40.4	41.6
12	24.4	30.6	33.6	35.6	36.4	38.0
13	21.8	27.4	30.2	31.8	33.4	34.6
14	19.4	24.8	27.2	29.0	30.2	31.4
15	17.3	22.4	24.6	26.3	27.4	28.7
16	15.5	20.0	22.2	24.0	24.8	26.1
17	13.9	17.8	20.0	21.7	22.6	23.8
18	12.4	16.0	18.0	19.8	20.4	21.5
19	11.1	14.4	16.2	17.7	18.4	19.7
20	9.9	13.0	14.6	16.0	16.8	17.7
21	8.9	11.6	13.4	14.6	15.2	16.1
22	7.7	10.4	12.0	13.0	13.8	14.5
23	7.0	9.4	10.8	11.8	12.4	13.4
24	6.3	8.4	9.8	10.8	11.4	12.2
25	5.6	7.6	8.0	9.8	10.4	11.1

2. The large source diameter, 1¼ inches, required by the low specific activity of the cesium chloride, 22.4 c/g, made additional collimation a necessity.

TABLE V

HALF-VALUE LAYERS AND ABSORPTION COEFFICIENTS FOR CESIUM 137 GAMMA RAYS

Material	Half-value Layer mm.	Linear Absorption Coefficient $cm.^{-1}$
Aluminum	35.0	0.198
Copper	11.25	0.616
Lead	5.35	1.295
Mix-D	81.6	0.085
Water	83.5	0.083

3. The low output of the source, 8 trmin. at one meter, forced a change of r/eatment distance from 75 cm. to 50 cm. source skin distance.

4. The electronic equilibrium thickness of tissue equivalent material was found to be 1.4 mm.

5. Percentage depth dose, exposure dose and absorbed dose rates are given for 22 treatment fields.

6. Comparison of cesium 137 and cobalt 60 isodose curves is made for 3 typical field sizes, with the finding that in general the shapes of the curves are quite similar, but that the cobalt holds a definite advantage

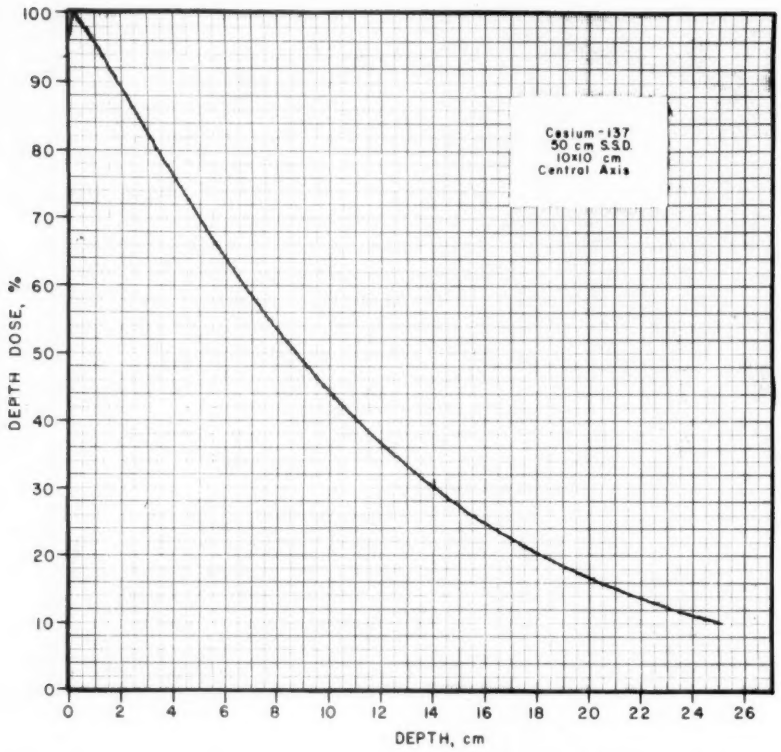

FIG. 13. Central axis depth dose as a function of depth for a 10×10 cm. field at 50 cm. SSD.

over the cesium from the standpoint of its greater depth dose.

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EFFECT OF RADIOGOLD 198 IN THE TREATMENT OF FIBROMYXOSARCOMA WITH CYST FORMATION*

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HOUSTON, TEXAS

RADIOGOLD 198 has been used extensively for the palliation and, in some instances, prophylaxis of malignant effusions into both the pleural and peritoneal cavities with 30 to 80 per cent relief in patients with carcinoma of the lung, colon, ovary, and prostate.[1,2,4,5,8–11] No reports have been found by us of its use in fibrosarcoma complicated by myxomatous change and fluid accumulation. The case reported here was treated with Au^{198} on two occasions in an effort to control fluid accumulation in a cystic fibrosarcoma located in the soft tissues of the buttock.

REPORT OF A CASE

An eighty year old white male, retired salesman, was admitted for the fifth time to the Veterans Administration Hospital, Houston, Texas, on May 1, 1957, with pain in the left hip radiating down the posterior thigh to the calf, of six months' duration. Past history included multiple admissions to this and other hospitals for chronic prostatitis, adenocarcinoma of the bladder, chronic bronchitis, senile emphysema, arteriosclerotic heart disease with left bundle branch block, calculus in gallbladder, and cataract. In 1947, at another hospital, the patient had a large cystic mass removed from the left shoulder. This arose beneath the skin and extended forward, around, and underneath the infraspinatus muscle and was filled with dark fluid and soft tissue. It was reported as a "sarcoma from the back, nonpigmented malignant melanoma." There has been no local recurrence since the operation. Physical examination revealed a slight limp favoring the left hip on walking and the presence of a discrete, firm soft-tissue mass, 6 cm. in diameter, over the left femoral neck anteriorly. A less well-defined mass was palpated in the left gluteal region. No lymph node enlargement was noted. The remainder of the physical examination was unremarkable. Routine blood studies were within normal limits. Liver function tests were normal except for a bromsulphalein retention of 16 per cent in thirty minutes. Urinalysis revealed a trace of albumin and 40 to 45 white blood cells per high power field on microscopic examination. Roentgenographic examination showed emphysematous changes of the lungs, mild osteoarthritic changes of the lumbar spine, and minimal narrowing of the joint space of the left hip. Examination of the colon was negative.

Exploration of the anterior thigh was performed in an effort to biopsy the mass which had been palpated, but no abnormal tissue was found. Consequently, a biopsy was taken from the left gluteal mass and a histologic diagnosis of "myxosarcoma" obtained. On June 14, 1957, excision of the mass was attempted under spinal anesthesia. A curvilinear incision was made in a skin crease of the left buttock and carried through the subcutaneous tissue and deep fascia to expose a globular mass approximately four inches in diameter just beneath the deep fascia. This mass was soft, grayish-white and appeared to be well encapsulated. The sciatic nerve which was tightly stretched across the mass was carefully dissected free. Dissection was carried to the region of the hip joint, at which point it was found that the lesion was firmly adherent to the bony pelvis and to the joint capsule. In addition, a tongue of tumor curved anteriorly, winding around the neck of the femur. Because of this extension it was felt that complete removal would require a hemipelvectomy. This extensive operation was deemed inadvisable in this elderly patient; consequently, a local excision of the portion of the mass which protruded into the buttocks was performed, leaving the portion attached to the pelvis and the tongue which extended anteriorly. It was hoped that this partial removal of the tumor would produce some symptomatic relief. The specimen consisted of 6 portions of rather firm, gelatinous tissue up to 5 cm. in greatest diameter. The cut surfaces were light gray and shiny. Microscopic

* From the Radioisotope Laboratory, and the Surgical Services of the Veterans Administration Hospital, Houston, Texas, and the Department of Radiology, Baylor University College of Medicine, Houston, Texas.

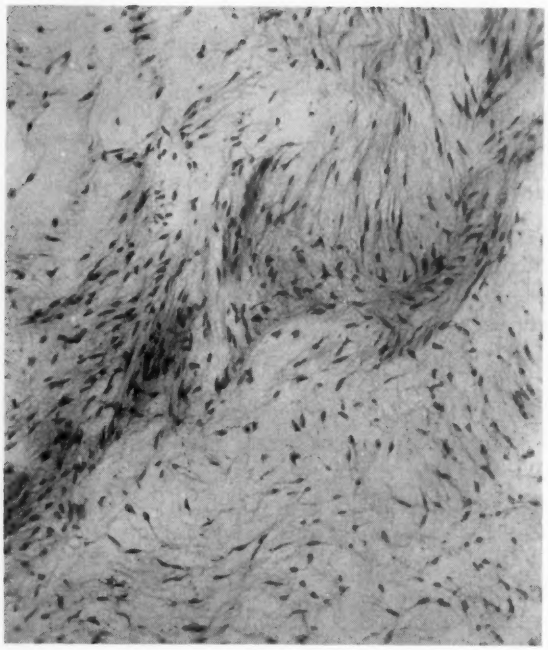

Fig. 1. Microscopic appearance of tumor removed at operation on June 14, 1957, revealing delicate spindle-shaped neoplastic cells. A diagnosis of fibromyxosarcoma was made.

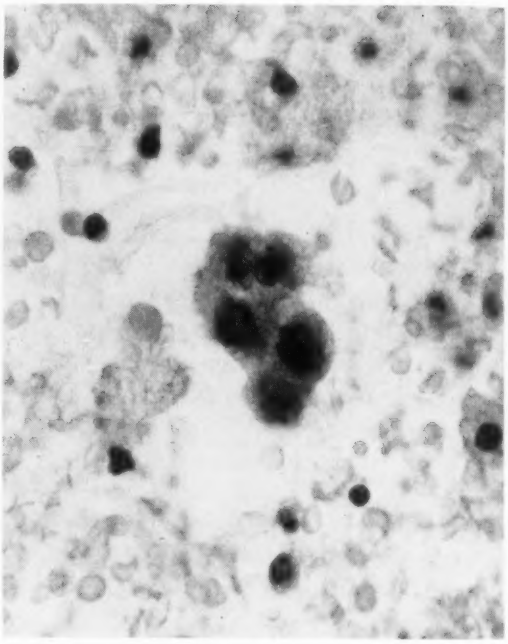

Fig. 2. Cell block preparation of fluid removed from the cystic mass of the left buttock prior to instillation of Au^{198}.

examination revealed delicate spindle-shaped neoplastic cells having a stream-like pattern. Most of the nuclei were small, oval, and deeply stained with the cytoplasmic processes of the cells fading into a pale ground substance. A diagnosis of fibromyxosarcoma was rendered (Fig. 1).

Postoperative recovery was essentially uneventful except for drainage of dark material from the wound. Between June 25, 1957, and July 10, 1957, an elapsed time of fifteen days, a dose of 3,000 r was delivered through 4 converging fields, 6 by 6 cm. at a depth of 7 cm., by Van de Graaff 2 mev. radiation. Following this treatment, the patient was discharged from the hospital. The mass disappeared for four months but recurred in November, 1957, at this time being fluctuant. Aspiration produced viscous material containing neoplastic cells (Fig. 2) and repeat paracenteses of 60 to 100 cc. were necessary at least every two weeks for control of pain. On January 6, 1958, the patient was readmitted to the hospital with physical findings essentially unchanged except for a mass in the left buttock (immediately beneath the scar of previous operation) that was fluctuant and minimally tender. There was slight hyperpigmentation of the area of the scar.

On January 8, 1958, 20.3 mc of Au^{198} in 10 cc. total volume was injected into the cystic mass of the left buttock through a polyethylene catheter (threaded through a No. 15 gauge needle) in an attempt to control the production of fluid. Serial blood studies revealed no change in the white blood cell count, differential count, hemoglobin, hematocrit, and platelet count for two months following this first injection. Liver function tests disclosed minimal changes in cephalin flocculation varying from negative to 2+ during the first fourteen days following injection. Serial scintigrams showed good localization and distribution of the radiogold in the cystic mass of the left buttock (Fig. 3) and very little translocation of Au^{198} to the liver. Blood assays and urinary assays as shown in Figures 4 and 5 demonstrated minimal reabsorption of the Au^{198} from the cystic mass. Repeat aspiration on January 22, 1958, produced 100 cc. of rusty mucinous material containing 33 μc of Au^{198}. Microscopic examination disclosed neoplastic cells stippled with black granules, presumably mercury or gold (Fig. 6). For two months following treatment, aspiration was necessary at two week intervals. On March 5, 1958, a second dose of 50 mc of Au^{198} in 4 cc. total volume was injected into the cystic mass, and on March 12, 1958, supervoltage (Van de

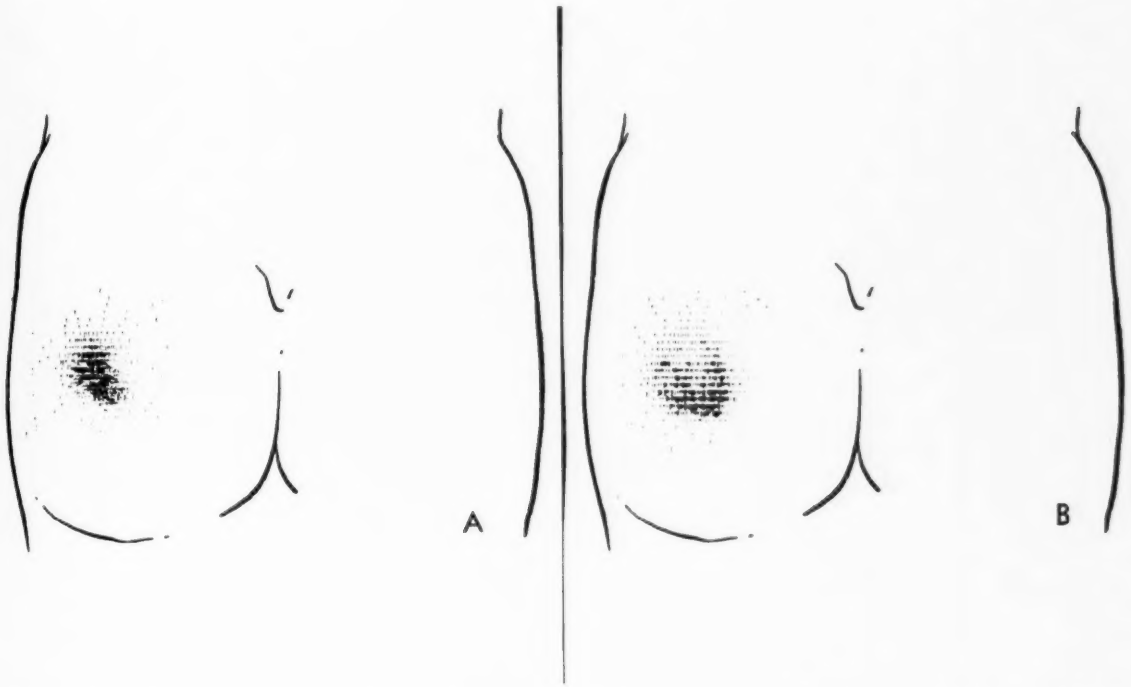

Fig. 3. Scintillation scans done (*A*) immediately and (*B*) fourteen days after injection of 20.3 mc of Au[198] into the cystic mass of the left buttock, showing localization of radiogold within the cystic cavity.

Graaff) roentgen therapy was begun with the aim of delivering 2,000 r at a 7 cm. depth in seven days through 4 converging fields 6 by 6 cm. in size. Four days following the completion of roentgen irradiation, the area became markedly indurated and the skin intensely erythematous, but this response subsided within seven days without sequelae. No change in blood cell count or liver function occurred. The results of the urine and blood radioassay following injection are given in Figures 5 and 7. Scintigrams immediately and twelve days after injection are shown in Figures 8 and 9. As long as three months after the second injection and two and one-half months after the completion of roentgen therapy, the patient required aspiration of the cyst for pain control only once a month. Aspirations were productive of 30 to 60 cc. of clear yellow mucinous material. However, thereafter, aspiration again became necessary at one to two week intervals.

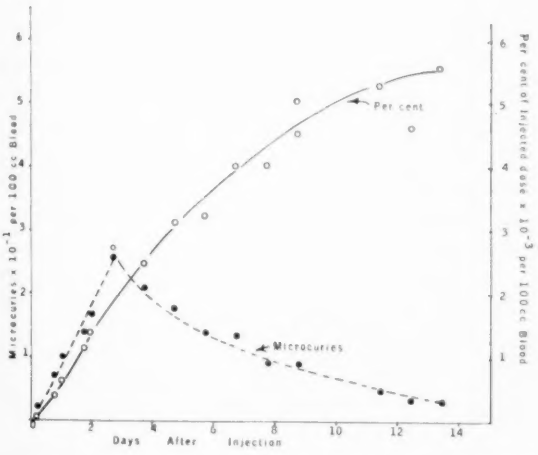

Fig. 4. Percentages of injected dose and radioactivity in microcuries per 100 cc. of blood were determined serially after injection of 20.3 mc of Au[198] into the cystic cavity on January 8, 1958. This determination reveals a prompt fall in blood radioactivity following the initial rise for two to four days.

DISCUSSION

While the behavior of radiogold 198 instilled into serosal cavities and into solid tumors is known, there was no information available prior to this case as to the translocation and absorption of Au[198] from a malignant cystic mass. We estimated the cystic cavity to have a volume of 30 cc. with a surface area of about 43 cm.^{2}. By our

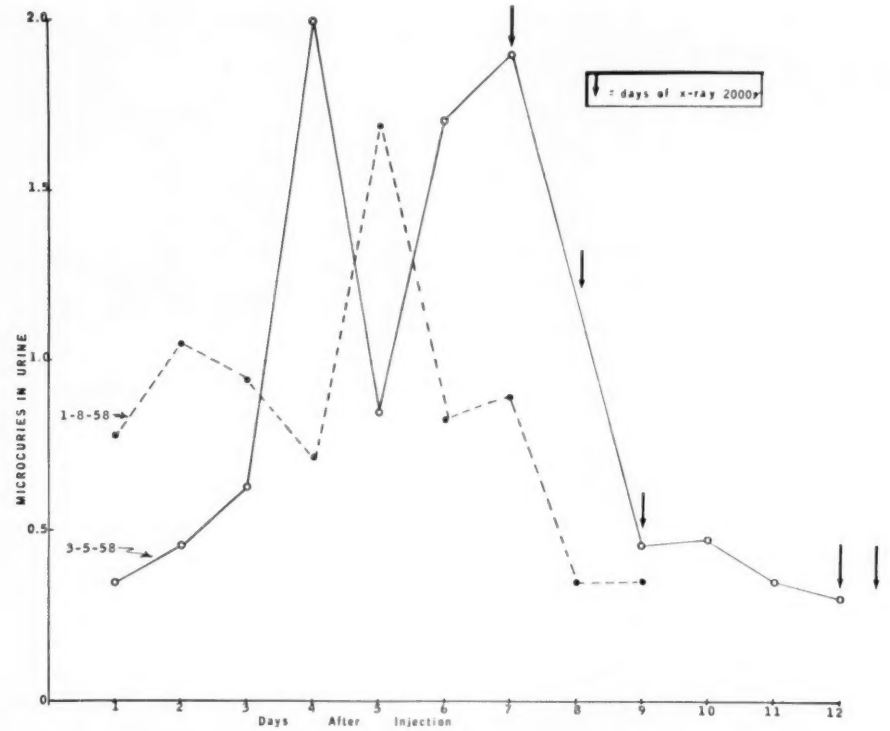

Fig. 5. Urinary excretion of Au^{198} in twenty-four hour urine collection following the injection of 20.3 mc on January 8, 1958, and 50 mc on March 5, 1958. Following the second injection roentgen therapy to the cystic mass was begun and completed in seven days.

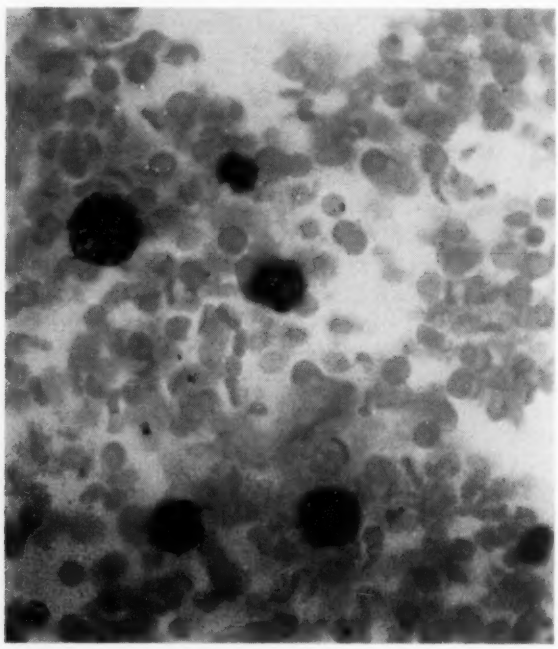

Fig. 6. Cell block preparation of fluid removed from cystic cavity two weeks following the first injection of Au^{198}. This demonstrates the stippling of the neoplastic cell with black granules.

calculations from the lipiodol study (Fig. 10 and 11), and the above, the initial Au^{198} dose of 20.3 millicuries should have delivered at least 40,000 rep to the tumor surface.* This dose is likely to be smaller than the actual dose since the thickness of the tumor wall and the amount of material deposited on the surface were unknown; and, furthermore, an additional surface area might have been contributed by invagination of the tumor into the cavity.[3] The second dose of 50 millicuries should have delivered at least 40,000 rep to the tumor surface (based on an estimated cavity size of 100 cc. and a surface area of about 120 $cm.^2$).* The tumor cells sloughing into the cavity showed some effect of the Au^{198} following both the first and second injections. The roentgen irradiation was added to attempt destruction of the tumor "rind" in the outer portions of the mass. This at-

* Calculations were based on formulae and data of Marinelli, Quimby, and Hine[6] and geometry factors of Quimby.[7]

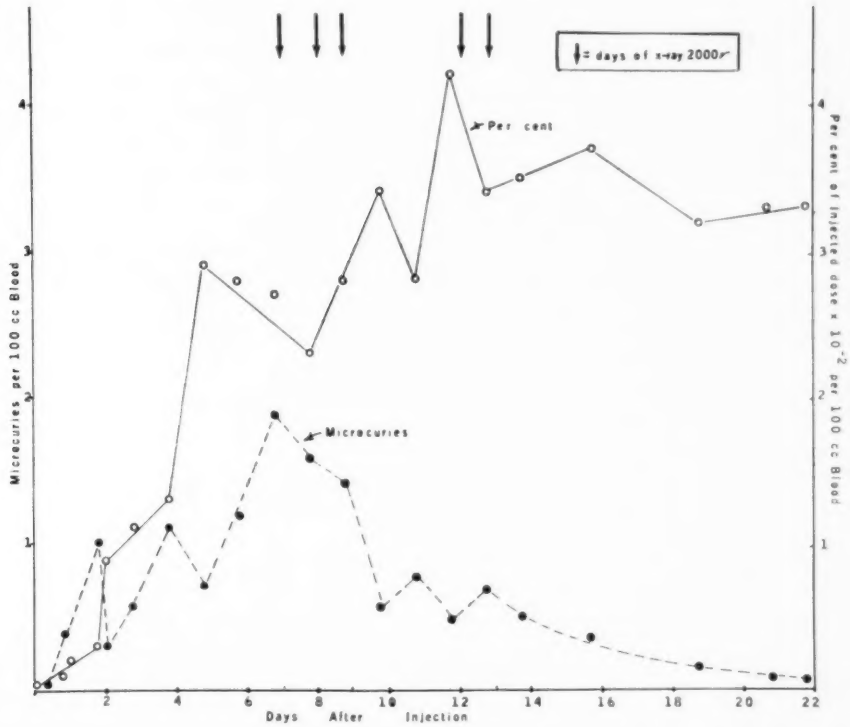
= days of x-ray 2000r
Per cent
Microcuries
Microcuries per 100 cc Blood
Per cent of injected dose x 10^-2 per 100 cc Blood
Days After Injection

FIG. 7. Percentages of injected dose and radioactivity in microcuries per 100 cc. of blood were determined after the injection of 50 mc of Au[198] on March 5, 1958. The rise in blood radioactivity was more prolonged following the second injection than the first, but fell to negligible amounts by the fourteenth day. Possible tissue damage with subsequent increase in blood absorption of radiogold may have occurred as a result of roentgen therapy given on the days indicated by black arrows.

FIG. 8. Scintillation scans of the (*A*) buttock and (*B*) liver area immediately after the second injection of 50 mc of Au[198] on March 5, 1958. This demonstrates good localization within the cystic mass of the left buttock and no significant radioactivity above the level of body background in the liver.

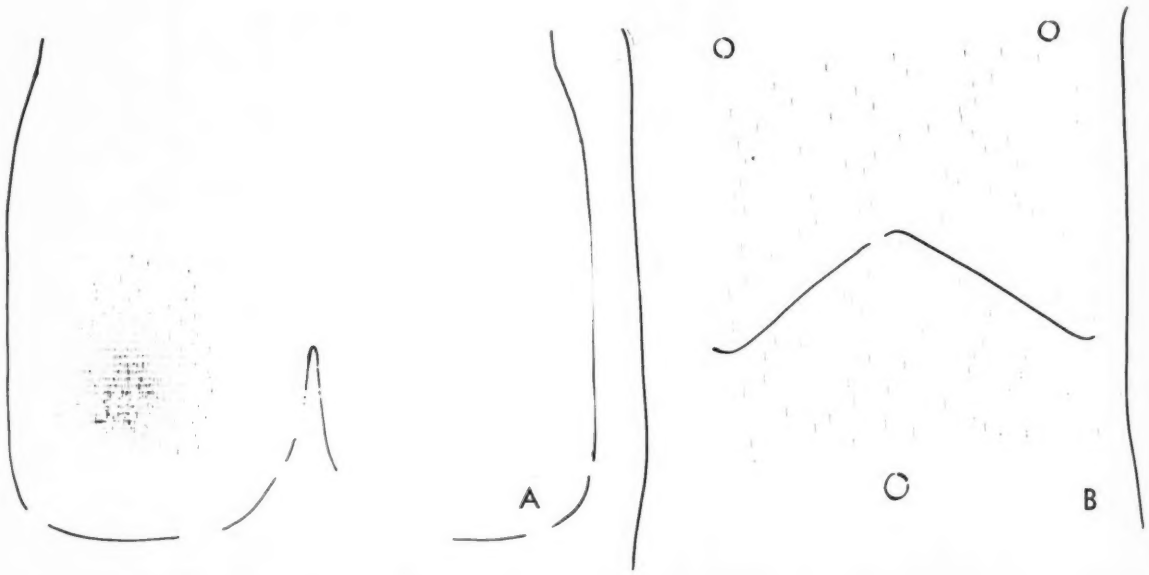

Fig. 9. Scintillation scans of the (*A*) buttock and (*B*) liver area twelve days after the second injection of 50 mc of Au^{198} on March 5, 1958, demonstrating continued localization of radiogold in the cystic mass of the left buttock.

Fig. 10. Anteroposterior roentgenogram of the femur and pelvis following the injection of lipiodol into the cystic mass of the left buttock.

Fig. 11. Lateral roentgenogram of the femur and pelvis following injection of lipiodol into the cystic mass.

tempt thus far has been only partially successful in that fluid re-accumulation in the tumor decreased temporarily, making aspiration necessary at intervals of four to six weeks for three months and at intervals of one to two weeks thereafter. Neoplastic cells containing black granules continue to be found in the fluid. Further observation of this case will be necessary for a final decision as to effectiveness; however, information derived from blood assay and serial scintigrams reveals that practically no absorption or translocation of Au^{198} occurs from injection into such a cystic cavity.

SUMMARY

Radiogold 198 has been used in a cystic fibromyxosarcoma of the left buttock. No significant absorption and no deleterious effects were noted. Temporary decrease in the rate of fluid re-accumulation was obtained after the second injection combined with external supervoltage roentgen therapy.

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TRANSSPHENOIDAL DESTRUCTION OF THE HYPOPHYSIS WITH RADIOACTIVE YTTRIUM*

By R. D. MOSELEY, Jr., M.D., W. M. S. IRONSIDE, M.D., PAUL V. HARPER, M.D., *and* ALICE McCREA, S.M.
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THIS report concerns the technique of pernasal transsphenoidal Y^{90} implantation of the pituitary gland using biplane fluoroscopic image intensifier control. Some preliminary results of destruction of the hypophysis in a group of 50 patients with metastatic breast or prostate cancer are presented. Theoretical considerations leading to the development of this technique, the present status of the technique itself, and the incidence of complications are discussed in detail. Brief reference is made to comparative results obtained by other methods of hypophysectomy.

Based on the work of Huggins[3] and others, the endocrine influence on the metabolism of certain neoplasms, notably those arising in the breast and prostate, has been well established. Luft, Olivecrona, and Sjögren[9] introduced surgical hypophysectomy as an endocrinologic method for the control of breast cancer. There can be no doubt that this procedure will produce remissions in some cases.[10,11] Several methods for the introduction of various radioactive materials into the sella turcica for destruction of the pituitary gland have been described.[1,2,12] There is evidence to indicate that ablation of the hypophysis can be obtained with relatively high doses of externally administered proton beam radiation.[7] Sufficiently high doses of radiation to the pituitary gland cannot be achieved with ordinary external roentgen therapy.

Because of the difficulty of achieving complete surgical removal of the pituitary gland,[10,12] it was felt that the destructive action of radiation might offer more complete ablation. Since the use of radon[2] involves the irradiation by gamma rays of numerous important structures in close proximity to the pituitary gland, the employment of discrete sources of beta radiation, such as those described by Kisieleski, Svihla, and Brues,[6] was elected. Based on dosimetric considerations, the number of discrete beta sources was set at 6 to 10 rather than the smaller number which has been used by others;[1] the mechanical introduction of more than this number of localized sources presents practical problems. The inhomogeneity in dose is greatest from localized beta particle sources if the volume occupied by the localized sources is small and the size of the source is large.[8] Inasmuch as the minimum beta particle dose may be much smaller than the average beta particle dose if the localized sources are far apart in relation to the tissue absorption (so that a more ideal distribution is represented by a homogeneously distributed colloidal suspension with a minimum beta dose only a few per cent below the average beta dose), when using such localized sources, it is obligatory from the point of view of good dosimetry to introduce as many small pellets as practicable. The theoretically ideal solution to the problem —the injection of radioactive colloidal material, such as Au^{198} or $CrP^{32}O_4$—is not satisfactory due to the fact that the particles will not remain at the site of injection but will spread to affect adjacent vital structures. If this were not the case, it is probable that the retention of the radioactive colloidal particles in the needle tracts would result in a distribution of radiation equal to but not better than that obtained by discrete sources. Because of the operative risk in patients with extensive meta-

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static disease, as well as the difficulty of achieving adequate distribution of the radioactive pellets, the transcranial route[5] has now been supplanted in our laboratory by the pernasal transsphenoidal approach performed with biplane fluoroscopic image intensifier control. The implant is designed to deliver a minimum dose of 200,000 rad to all of the volume of the pituitary gland, since experimental evidence indicates that such a dose range is necessary to produce necrosis of the gland.

Yttrium 90 has many characteristics which make it the most suitable isotope for this technique. It has a strong beta radiation (E_{max} 2.3 mev.), short half life (64 hours), and Y^{89} has an adequate activation cross section for thermal neutrons (1.24 barns) (Fig. 1). Small cylindrical pellets (17 gauge), weighing approximately 4 mg., are produced by compressing $Y_2{}^{89}O_3$ powder in a mold and then sintering them in an alumina crucible at 1650°C. for one hour, converting them to solid ceramic material (Fig. 2). Activities of 0.7 to 1.0 mc per pellet are obtained by placing them in a thermal neutron flux of 3×10^{13} N/cm.^{2}/sec. for four to five hours. The activity is determined by dissolving a test pellet in nitric acid and counting an aliquot under conditions of known geometry. Since the pellets are not radioactive during the process of fabrication, many manufacturing difficulties are avoided.[6] While the maximum range of the beta particles from yttrium 90 in tissue is about 1 cm., a significant radiation dosage is not encountered farther than 4 or 5 mm. from the pellet (Fig. 3). Pellets of the size described may be brought to such levels of specific activity that four or five days could elapse between activation and utilization; thus, there is no limitation on potential availability of the radioactive yttrium for this procedure.

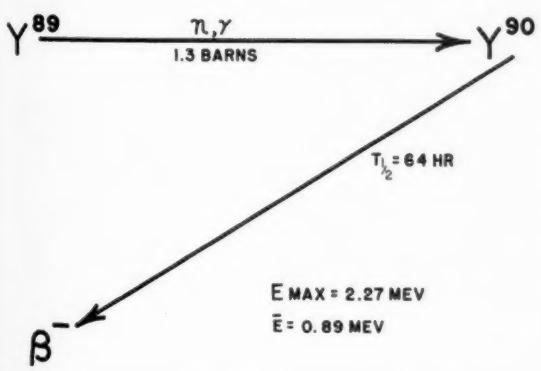

Fig. 1. Nuclear chemistry involved in the fabrication of yttrium pellets.

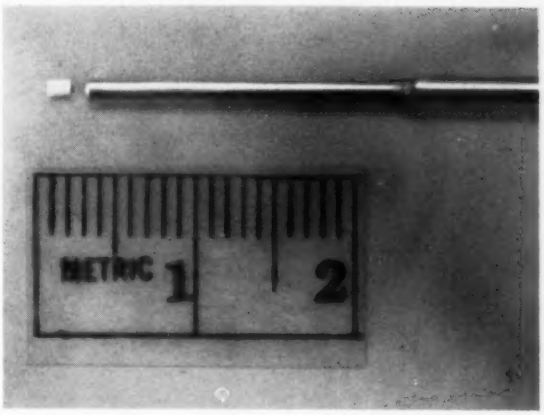

Fig. 2. A small cylindrical ceramic yttrium oxide pellet is placed at the tip of one of the needles used in the operative procedure.

TECHNIQUE

Following premedication with nembutal 150 mg. and demerol 100 mg., local anesthesia of the nasopharynx is induced with 10 per cent cocaine with adrenalin.[4] Radiopaque markers are placed on the patient's chin and on the vertex of the skull in order

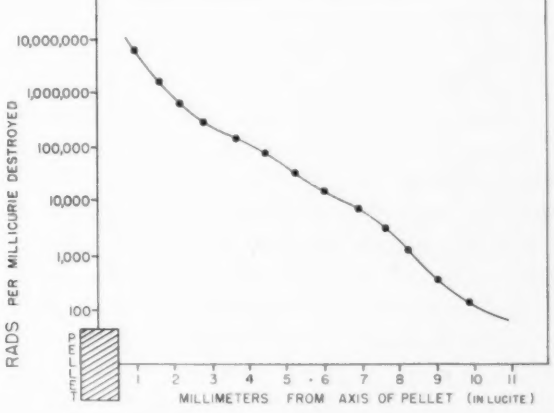

Fig. 3. Range of beta particles from an yttrium 90 pellet in tissue equivalent material.

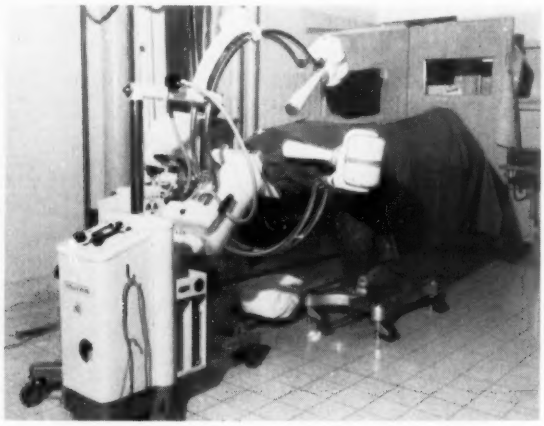

FIG. 4. Position of the portable image amplifier units for biplane viewing during the operative procedure.

to facilitate alignment of the skull under fluoroscopic control. The field is draped without the use of metallic clips which might interfere with fluoroscopic visibility. Two mobile Phillips image intensifier units (Mueller Surgex BV20) are positioned so that the radiologist can view the posterior nasopharynx, the sphenoid sinus and the sella turcica on the lateral screen and can visualize the base of the skull in a projection 90° from lateral on a screen placed at the vertex of the skull (Fig. 4). Special instruments for this technique are illustrated in Figure 5. The operator loads the Y^{90} pellets into their cartridges under water (11 mm. of water offers complete shielding against the beta particles).

A strengthened 17 gauge spinal needle is passed into the left nostril and guided to the medial part of the anterior wall of the sphenoid sinus. Under fluoroscopic image intensifier control, the position of the tip of the needle and its direction are checked before it is advanced into the sphenoid sinus. Penicillin-topical thrombin (1.5 cc. of a solution containing 10,000 units of penicillin and 200 units of thrombin per cc.) is introduced into the sinus. The tip of the needle is then advanced under fluoroscopic control into the posterior portion of the sella turcica medially. A posterior pellet is deposited (Fig. 6) and the needle tip withdrawn 4 mm. for placement of the anterior

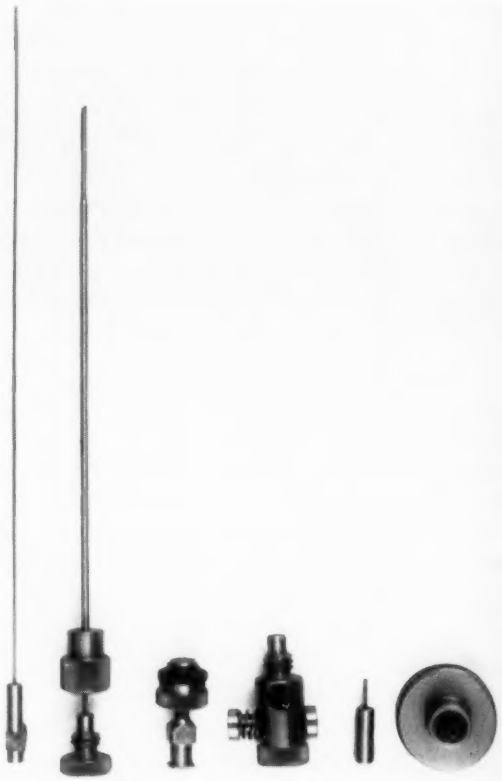

FIG. 5. Special instruments which have been developed for handling and introducing the pellets. (Reproduced by permission from *The Laryngoscope*, 1958, *68*, 711–725.)

pellet. The needle is then withdrawn into the sphenoid sinus directed approximately 4 mm. laterally and again introduced into

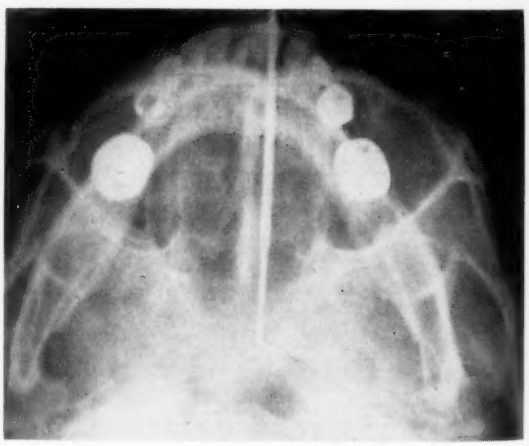

FIG. 6. Roentgenogram in the axial view made on the image intensifier unit, showing the needle in position and the posterior pellet in place.

the posterior part of the sella turcica. Posterolateral and anterolateral pellets are deposited. The procedure is repeated via the right nostril with depositions into the right half of the pituitary gland (Fig. 7). Variations in the size of the sella and in the accuracy of placement determine the total number of pellets required to achieve adequate distribution; 6 to 11 pellets have been used. Individual variations in size and position of the nasal and sphenoidal septa may result in modification of the planned approach but do not preclude accurate deposition. Following placement of the implants, roentgenograms are obtained for dosimetric determinations.

In order to estimate the roentgen-ray exposure dose received by the surgeon, radiologist and other operating room personnel during an implantation, isodose curves of scattered radiation around the Mueller Surgex BV20-Phillips image intensifier units were plotted. Since the machines are never in use simultaneously, there is no necessity for adding isodose curves from the two units. The total "beam on" time during the procedure is less than five minutes, the long cone (approximately 28 cm.) is used, and the field, at the position of the fluoroscopic screen, is 13 cm. in diameter. A Mix D head phantom was used as the scattering object and the roentgen tube was activated at the maximum setting of 75 kv. peak, 3 ma.

The measurements were made with a Juno radiation survey meter—Model SRJ-3. A Victoreen thin-nylon 250 r thimble chamber, which had been calibrated at the National Bureau of Standards, was used to calibrate the Juno meter at 50 kv. A substitution method was employed in which the thimble chamber was exposed first; then the beam was collimated to a 0.04 $cm.^2$ area and the Juno meter exposed. The calibration factor for the Juno meter was found from:

$$\frac{\text{Reading of Victoreen chamber in r/hr.} \times \text{calibration factor of Victoreen chamber}}{\text{Reading of Juno meter in r/hr.} \times \dfrac{\text{area of beam}}{\text{area of ionizing volume}}} = \text{factor of Juno meter}$$

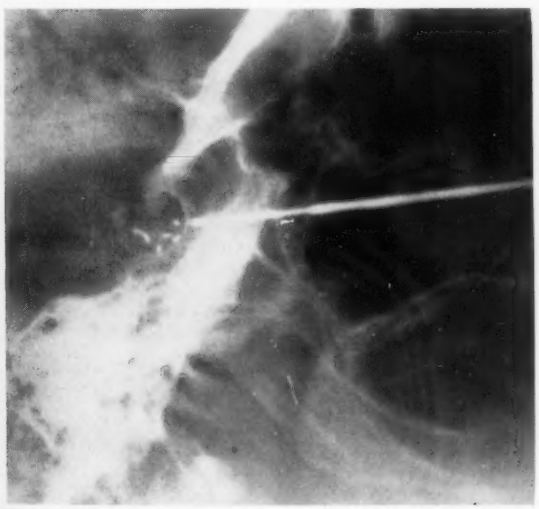

Fig. 7. Roentgenogram in the lateral view made on the image intensifier unit, showing multiple pellets in place in the pituitary gland. The tip of the needle has been withdrawn into the posterior portion of the sphenoid sinus.

The meter was found to read low by a factor of 2.3 with the beta shield closed and high by a factor of 1.8 with the beta shield removed.

Horizontal curves were plotted in the plane of the central axis of the primary beam on one side only, since the 50 cm. radius semicircular supporting arm of the image intensifier unit precludes occupation of the other side. Vertical curves were plotted in the plane of the 90° scattered beam and also of the 150° scattered beam where the surgeon normally stands. This position proved to be the position of maximum exposure. The isodose curves are reproduced in Figure 8, *A*, *B* and *C*.

Photographic dosimetric determinations of the dose of roentgen rays to which the operator's hands are exposed during fluoroscopic control of these procedures have re-

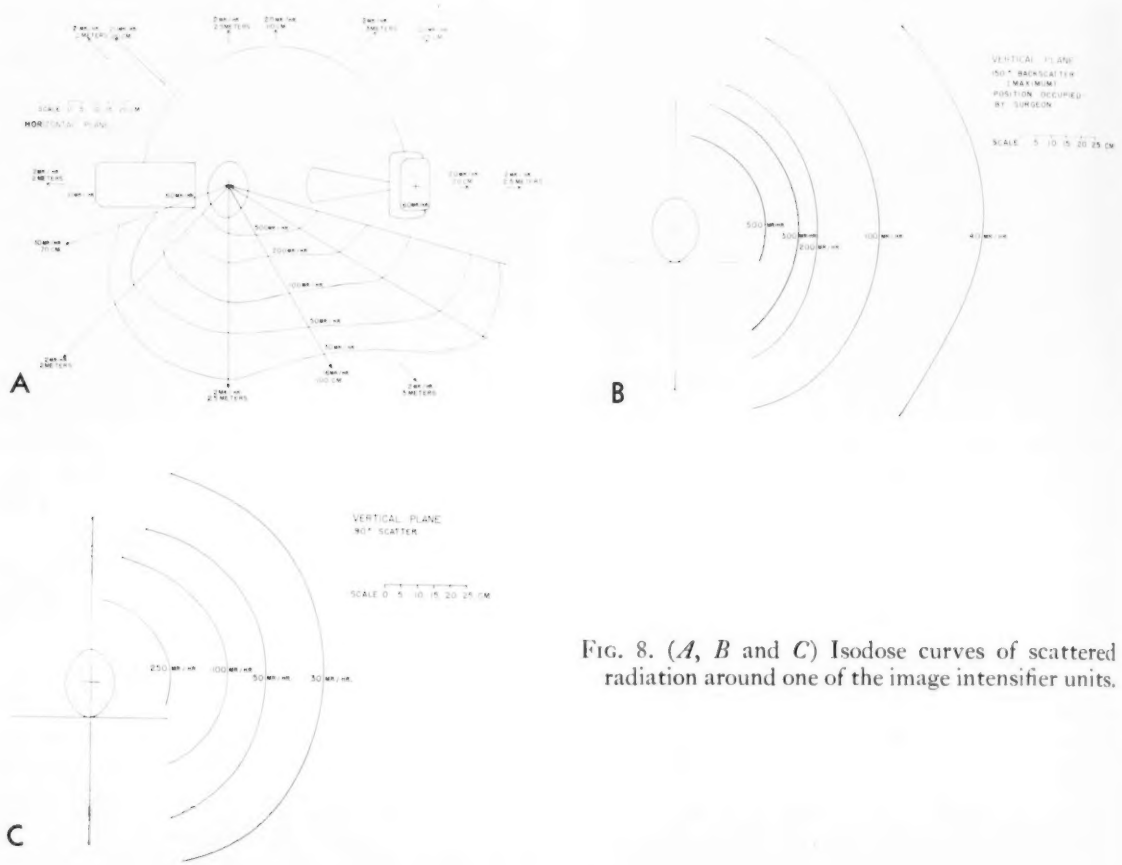

FIG. 8. (*A*, *B* and *C*) Isodose curves of scattered radiation around one of the image intensifier units.

vealed average doses of approximately 400 millirads. In order to keep the dose to the hands below the recommended permissible limit of 1.5 rad/week, an individual surgeon is limited to three operations per week. Of course, both surgeon and radiologist wear lead-rubber aprons of 0.5 mm. lead equivalent material, thus essentially eliminating concern in relation to total body exposure. Photographic dosimetric determinations of the doses to the outside of the protective aprons have demonstrated average doses of 20 millirads per procedure, well within the recommended permissible limits.

Because of the very short range of the beta particles and because the pellets are always handled under water by means of forceps or are encased in the shielding cartridges or needle, radiation from yttrium 90 presents no hazard at all in comparison to the potential hazards from the roentgen-ray control of the procedure.

RESULTS

Only preliminary conclusions as to the results of this method are justified at this time due to the short period of observation and small number of cases. Analysis is made of the results in 50 cases treated by means of pernasal transsphenoidal yttrium 90 implantation of the pituitary gland.

Of the 50 patients, 7 were male (6 with metastatic prostatic carcinoma; 1 with metastatic breast carcinoma) and 43 were female (41 with metastatic breast carcinoma; 2 with ovarian neoplasm). There were no operative mortalities. The results are presented in Table 1.

By objective evidence of beneficial effect of hypophysectomy is meant improvement in the roentgen appearance and size of lesions (Fig. 9, *A* and *B*), disappearance of subcutaneous metastatic nodules, decrease in effusion and ascites, and re-ossification of bone metastases (Fig. 10, *A* and *B*).

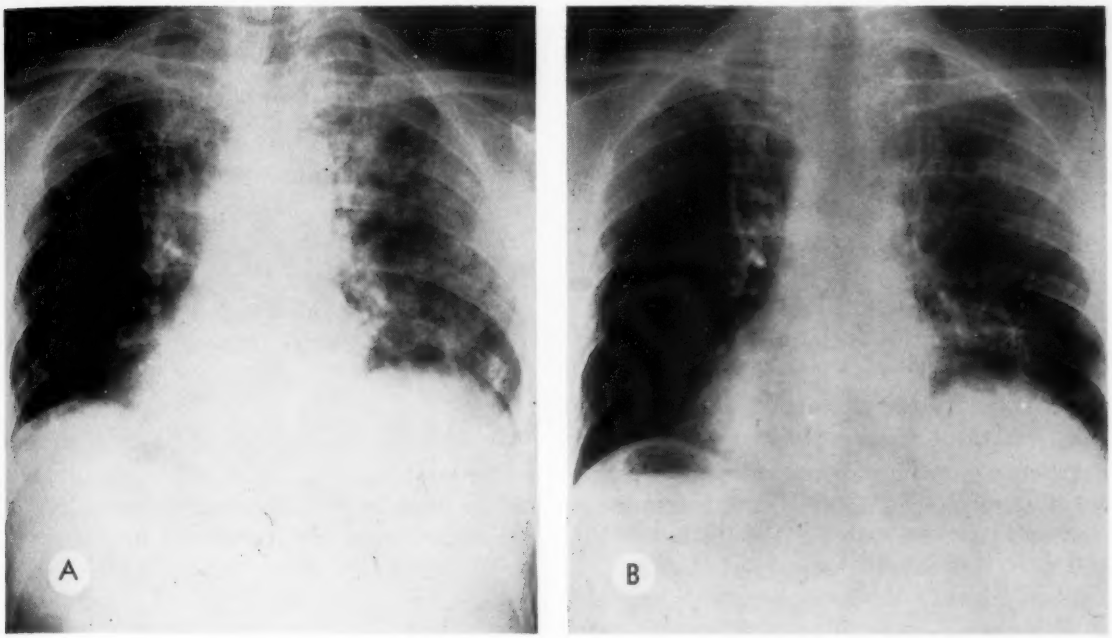

FIG. 9. Resolution of pulmonary metastases four months following hypophysectomy. (*A*) Immediately before hypophysectomy; (*B*) posthypophysectomy.

Relief of pain, weight gain, and improved sense of well-being are interpreted as subjective evidence of improvement.

Very quickly after hypophysectomy (within three to four days) pronounced decrease in twenty-four hour I^{131} uptake by the thyroid gland was demonstrated (Fig. 11). It has been noted, however, that there is no good correlation between fall in I^{131} uptake and response of the neoplasm to

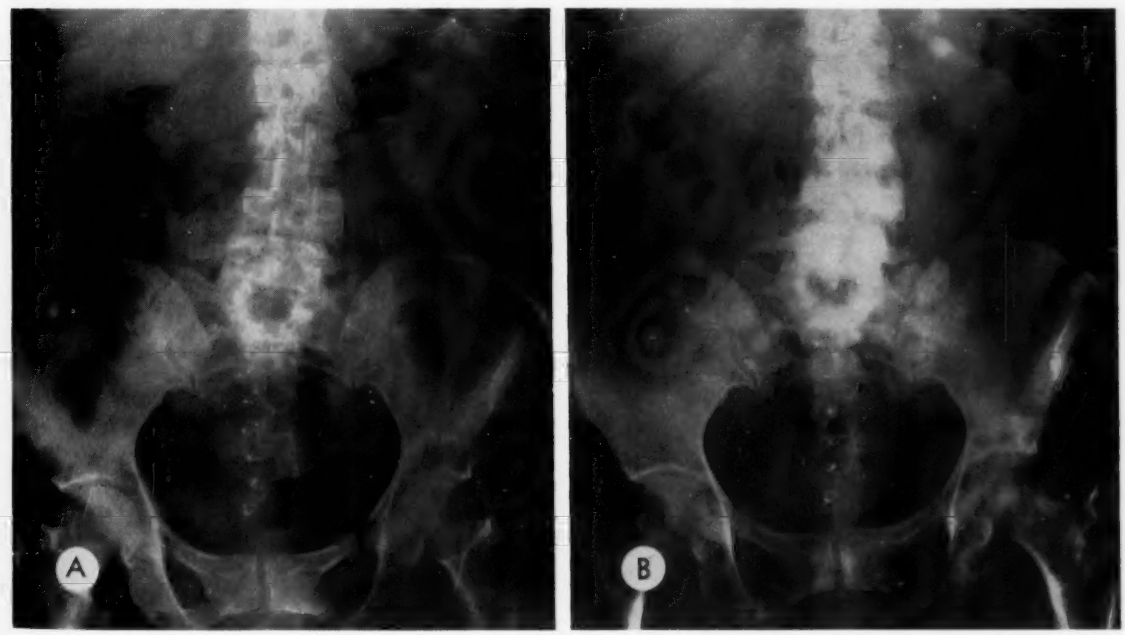

FIG. 10. Re-ossification of bone metastases. (*A*) Immediately before hypophysectomy; (*B*) five months posthypophysectomy.

TABLE I

CARCINOMA OF BREAST	
42 patients (41 females, 1 male)	
Subjective evidence of benefit	22
Objective evidence of improvement	11
Dead or no evidence of benefit	20
CARCINOMA OF PROSTATE	
6 patients	
Subjective and objective evidence of improvement	4
No benefit	2
CARCINOMA OF OVARY	
2 patients	
No benefit	2

hormonal ablation; *i.e.*, while the efficiency and extent of hypophysectomy can be determined by the demonstration of decrease in I^{131} uptake, no prognostic information can be deduced. Patients with no remission and patients with both subjective and objective improvement have all demonstrated fall in twenty-four hour I^{131} thyroid uptake.

On the other hand, patients with elevated serum alkaline phosphatase levels due to bone metastases showed alterations in the level of this enzyme following hypophysectomy (Fig. 11), and these variations do have prognostic significance; fall in serum alkaline phosphatase accompanies remission while subsequent elevation accompanies recrudescence.

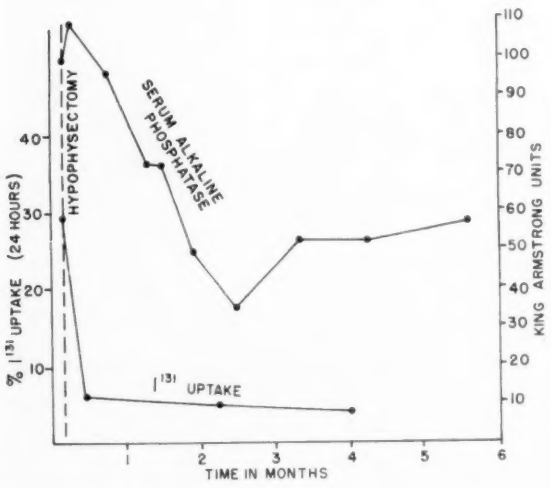

FIG. 11. Effect of yttrium 90 hypophysectomy on I^{131} uptake and on serum alkaline phosphatase level.

TABLE II

COMPLICATIONS	
Extraocular palsies	18
Cerebrospinal rhinorrhea	12
Meningitis	6
Anesthesia of the face	1
Embolization of pellets	1

COMPLICATIONS

Incidence of complications is indicated in Table II. The absence of operative mortality by this method is noteworthy. It can probably be largely attributed to the use of local rather than general anesthesia in these patients, many of whom are severely debilitated as a result of advanced metastatic disease.

There was one instance of third cranial nerve damage; 2 cases of paresis of the fourth cranial nerve; 3 patients with sixth nerve involvement. Combined nerve damage (III and IV) occurred in 11 patients; in one case there was bilateral paresis of III and IV. In only one patient was there evidence of damage to the second cranial nerve (constriction of the visual field of one eye). Thus, in 18 of 50 patients there was evidence of radiation effect in nerves adjacent to the sella turcica.

Cerebrospinal rhinorrhea occurred as a complication in 12 patients. Meningitis has occurred in 6 of these patients.

In one patient during the operative procedure three yttrium 90 pellets entered the arterial circulation at the base of the brain and embolized one of the small branches of the middle cerebral artery on the opposite side from that of insertion and two small branches of the anterior cerebral artery on the same side. There were neither immediate nor long-term detrimental effects or symptoms as a result of this accident.

PATHOLOGY

Histologic sections made serially through the pituitary glands removed at autopsy

FIG. 12. Section of a pituitary gland removed at autopsy. There are viable cells in the dark area at the junction of the anterior and posterior lobes and also along one lateral margin. Serial sections through the entire gland, measured as described, showed 80 per cent destruction in this case.

(Fig. 12) were examined and the areas of destruction determined by planimetry. Average destruction in 14 glands examined postmortem was 91 per cent, including one case in which, because of incomplete implantation due to hemorrhage, destruction was only 51 per cent. Despite evidence of incomplete destruction, there were indications that beneficial effects were being achieved in these cases. Evaluation of this problem requires a longer period of observation and more material for study.

DISCUSSION

It is, of course, much too soon to make final evaluation of the clinical results of hypophysectomy by this method. However, certain preliminary conclusions seem valid.

The morbidity and mortality of craniotomy make the transcranial approach for either surgical or radiation hypophysectomy less acceptable for both patient and physician. As a matter of fact, many of the patients who withstood without difficulty the transsphenoidal approach would not have been accepted for transcranial surgery because of their age and general condition.

There can be no doubt that hypophysectomy will produce palliation in cases of endocrine-sensitive tumors. The problem is how to accomplish the ablation of the hypophysis in the surest, safest manner. The lack of operative mortality by the transsphenoidal yttrium 90 implantation technique recommends this approach; the complication rate is distressing but does not compare unfavorably with the complication rate of transcranial approaches. Moreover, because of recent modifications in the distribution of the pellets and great attention to avoid placing the pellets too far laterally, there has been decrease in the incidence of cranial nerve damage in this most recent group of patients. This has been accomplished without compromise in obtaining distributions of the radioactive pellets that should produce destruction of the pituitary gland.

Complete destruction of the pituitary gland was the aim of this method; it is apparent that this was not uniformly accomplished. On the other hand, there was evidence of favorable response, both in these cases and in those cases of prostate cancer reported by Fergusson,[1] without complete destruction of the pituitary gland. Moreover, it is probable that the extent of destruction is at least as great as the extent of removal possible by transcranial surgical techniques.

SUMMARY

The technique of transsphenoidal yttrium 90 implantation of the pituitary gland under biplane fluoroscopic image intensifier control is described. Principles of dosimetry, nuclear chemistry, and surgical and fluoroscopic technique are considered. Preliminary estimates of clinical response are presented; the types of complications and their incidence are discussed. The method promises to be the most innocuous, effective method of hypophyseal ablation.

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VOL. 82, NO. 4

THE CREATION OF DEEP CEREBRAL LESIONS BY SMALL BETA-RAY SOURCES IMPLANTED UNDER GUIDANCE OF FLUOROSCOPIC IMAGE INTENSIFIERS (AS USED IN THE TREATMENT OF PARKINSON'S DISEASE)*

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and PAUL V. HARPER, JR., M.D.
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THE creation of cerebral lesions in the control of abnormal movements and rigidity is one of the major neurosurgical interests of the present decade. The pyramidal tract has previously been sectioned at the cortex, the internal capsule, in the cerebral peduncles and in the spinal cord, but at present the main targets are the juxtapyramidal basal ganglia—the globus pallidus and the thalamus. The close proximity of these structures to one another demands a precision of destruction which will obviate inadvertent damage to structures other than the target (Fig. 1). Such precision will increase both the safety of the procedure and the accuracy of physiologic interpretation of the results.

Methods currently in use are chemical cautery,[2] electrical cautery,[7] surgical ablation[1] and ultrasonic destruction.[3] Alcohol spreads back along the needle track and irregularly into tissue planes. Introduction of a balloon tipped catheter which creates a bed for the alcohol is an improvement, but from a physiologic point of view is inexact in that the extent of the chemical paralysis beyond the walls of the cavity and the surrounding damage by distortion of fiber tracks are impossible to measure. Electrical cautery, though extensively used in small animals, has not in our hands produced consistent lesions. Surgical ablation beyond visual control has the capacity to cause internal capsular hemorrhage and does not easily recommend itself. Ultrasound can create specific lesions but has a significant disadvantage over the other methods in that it requires a craniotomy instead of a burr hole.

These sources of destruction (except the ultrasound) are applied at the end of a needle or other slender instrument which may be directed to the target by roentgenographic or by stereoscopic guidance. The latter has no inherent advantage because, unfortunately, the heads of our patients are not standard; they are long and short, broad and narrow, high and low. Their brains, particularly in the elderly group, may show amazingly different degrees of atrophy. It is only necessary to section 10 human brains and measure point to point distances in the region of the basal ganglia to realize that no fixed system of coordinates, external or internal, will allow the operator to arrive stereotactically at a

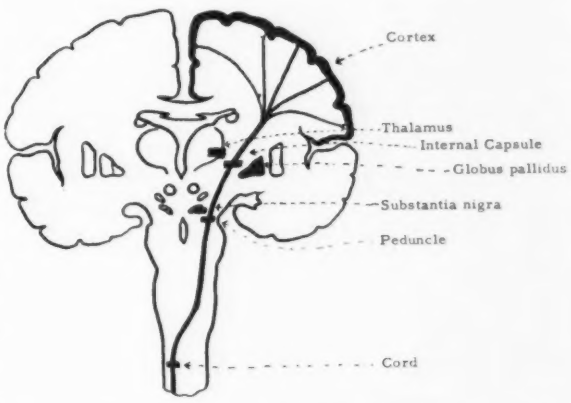

FIG. 1. Diagram of various sites of surgical attack in the treatment of Parkinson's disease.

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This work has been aided by a grant from the Simms Foundation.

given target in all cases. Stereotaxic instruments, irrespective of the skill of construction and manipulation, because of biologic variations can direct the source only to the presumed target.

The ideal technique must be simple, safe and under perfect control at all times. The lesion should develop slowly so that, should any undesired change commence, its presence can be detected at an early removable stage. Experience with the use of beta emitting isotopes over several years and with the image intensifier roentgen ray machines for a shorter period has suggested to us that a beta emitting source placed on the target under the guidance of biplane image intensifiers would provide an approximation to the ideal technique which we sought.

Palladium 109 was chosen because of its short half life (13.5 hours) and the convenient metallic form in which it is available. In animals wire sources 3 mm. long and weighing 2.8 mg. with an activity of approximately 20 mc will produce lesions which are first visible after forty-five minutes irradiation and will reach their maximum of 5–6 mm. diameter in ninety minutes (Fig. 2). A small amount of swelling may be noted during the following week but there is no extension of the histologic lesion over a period of a two year observation.[5]

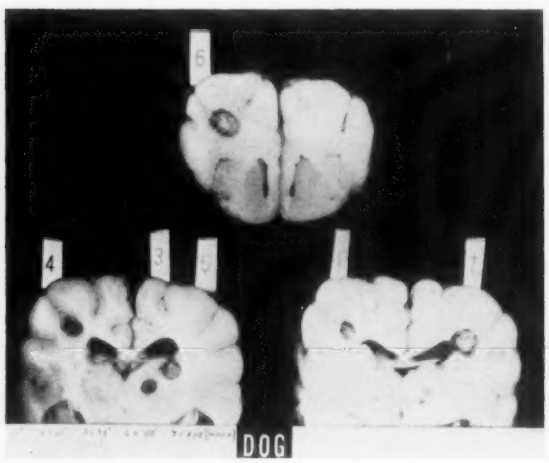

Fig. 2. Lesions produced by Pd^{109} (20 mc) in dog. Duration of application: (3) forty-five minutes, (4) sixty minutes, (5) seventy-five minutes, (6) ninety minutes, (7) one hundred and five minutes. Animal sacrificed ten days later.

TECHNIQUE

The first problem is to relate the target to a fixed bony landmark—the tip of the posterior clinoid process. Twenty-five to thirty cubic centimeters of air are introduced into the lumbar or cisternal subarachnoid space without removal of fluid, and the anterior and posterior commissures, the floor of the third ventricle and often the mammillary bodies are identified. Using these reference points, the site of the chosen target is plotted and its distance from the tip of the posterior clinoid is measured in three dimensions. The tube to skull distance is 72 inches and a correction factor is not employed. A burr hole is then made in a convenient location (usually behind the hair line at 5 cm. from the midline).

Several days later, using local anesthesia, the isotope is implanted under the guidance of the image amplifiers (Fig. 3). These provide an enlarged image sufficiently

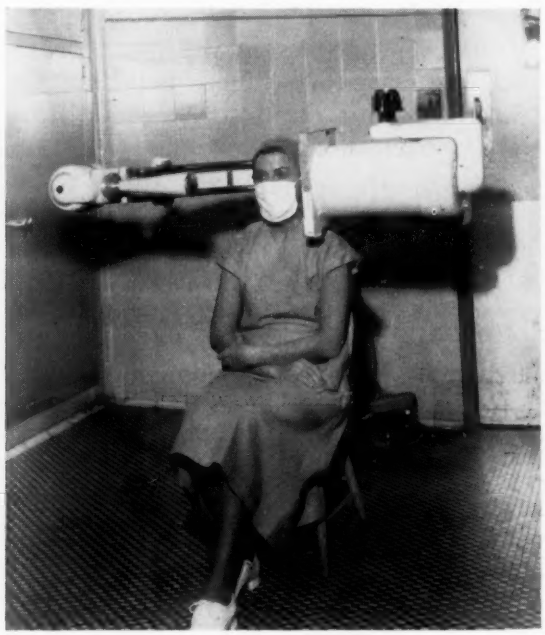

Fig. 3. "Surgex" image amplifier (Phillips). Two such instruments are used at right angles to one another to provide biplane visual control of insertion of the needle.

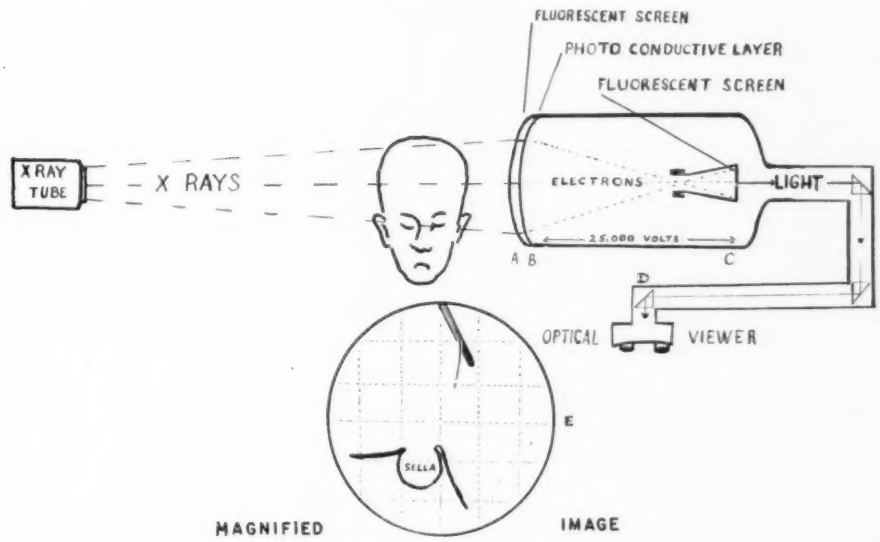

Fig. 4. Principles of the image amplifier. Roentgen rays fall upon fluorescent screen A causing light to strike photoconductive layer B. Electrons are emitted, accelerated by a 20,000 volt potential and condensed onto a small fluorescent screen C. This gives a bright image which is magnified and transferred by an optical system to the viewer D.

bright to be viewed without dark adaptation. The principles of these machines are outlined in Figure 4 and are well described in the literature.[4,6] The image of the introducing needle and sella turcica has, superimposed upon it, the image of a wire grid placed in front of the screen. By this means, point to point distances on the image are measured in grid squares, but to obtain the true dimensions of the object it is necessary to correct for divergent distortion. Since in these machines the target screen distance is fixed, the only variable is the object screen distance and the correction factor is readily obtained from a graph (Fig. 5). The chosen target is thus a precise number of grid squares or fractions thereof (corresponding to a precise number of millimeters) from the tip of the posterior clinoid process.

The small wire isotope 3 mm. long is placed in the tip of a plastic catheter under water (B. D. N444T). If the fit is loose, it is held in by bone wax. The active end of the catheter is introduced into the brain by means of a special needle fashioned from a No. 17 lumbar puncture needle (Fig. 6). The tip is solid and smooth. The catheter is extended through a hole which has been drilled in the side near the tip. By varying the distance and direction of protrusion of the catheter, a point anywhere within a centimeter of the line of axis of the needle

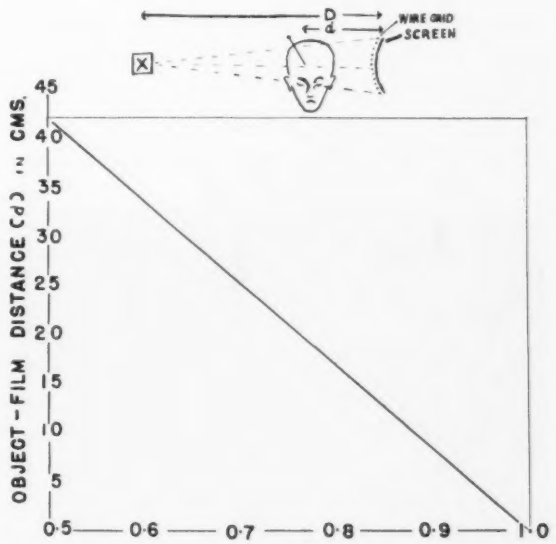

Fig. 5. Divergent distortion correction factor. By measuring the apparent dimensions of the image and multiplying by the correction factor, the true measurements of the object are obtained. Conversely, by dividing the true measurements by the correction factor, the apparent dimensions are obtained. The correction factor $= D-d/D$, where D is the target screen distance (83 cm.) and d is the object screen distance (varying from 0 to 40 cm.).

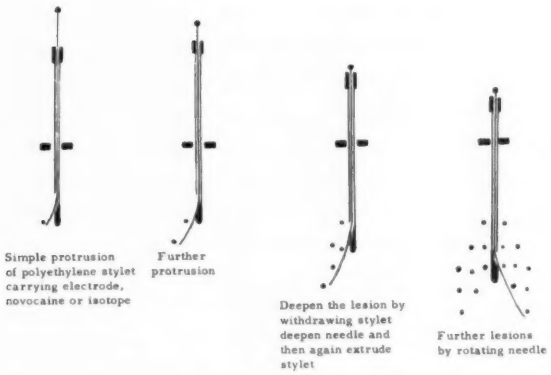
Simple protrusion of polyethylene stylet carrying electrode, novocaine or isotope
Further protrusion
Deepen the lesion by withdrawing stylet deepen needle and then again extrude stylet
Further lesions by rotating needle

Fig. 6. The versatile needle. By selective extrusion, any point within 10 mm. of the axis of the needle may be reached.

can be reached by the isotope. The initial placement of the needle need not, therefore, be absolutely accurate. Having guided it towards its target by fluoroscopic control, biplane roentgenograms are taken and the precise direction and extent of extrusion of the isotope are calculated and then accomplished.

As a rule, the mere placement of the needle has caused an alteration of function (*e.g.*, improvement of rigidity, tremor or both). More rarely, these changes advance while the isotope catheter and needle remain in place for ninety minutes. They have not been observed to advance beyond this period. If a more extensive lesion is required, the isotope is repositioned but, as a rule, this is not necessary. If symptoms return, as they sometimes do, a few days later a further lesion is made (Fig. 7).

In order to estimate the exposure dose received by the neurosurgeon, neuroradiologist and other operating room personnel during the procedure, isodose curves of scattered radiation were plotted and photographic dosimetry of chest, hand and ring badges was carried out. Although two machines are used in a biplane position, they are never "on" simultaneously and the total use of the roentgen-ray beam during the implantation is less than five minutes. Fluoroscopic factors are 75 kv. peak and 3 ma. The skin dose for the patient (entrance dose) is approximately the same as for a gastroduodenal examination (25 r). The dose outside the lead apron of the surgeon and radiologist averages 20 mr per procedure (recommended limits are 300 mr per week). Initially, the dose to the operator's hands during the needle insertion was 400 mr (permissible limit is 1,500 mr per week), but with experience we have found that it is unnecessary to have the hands in the field at any time.

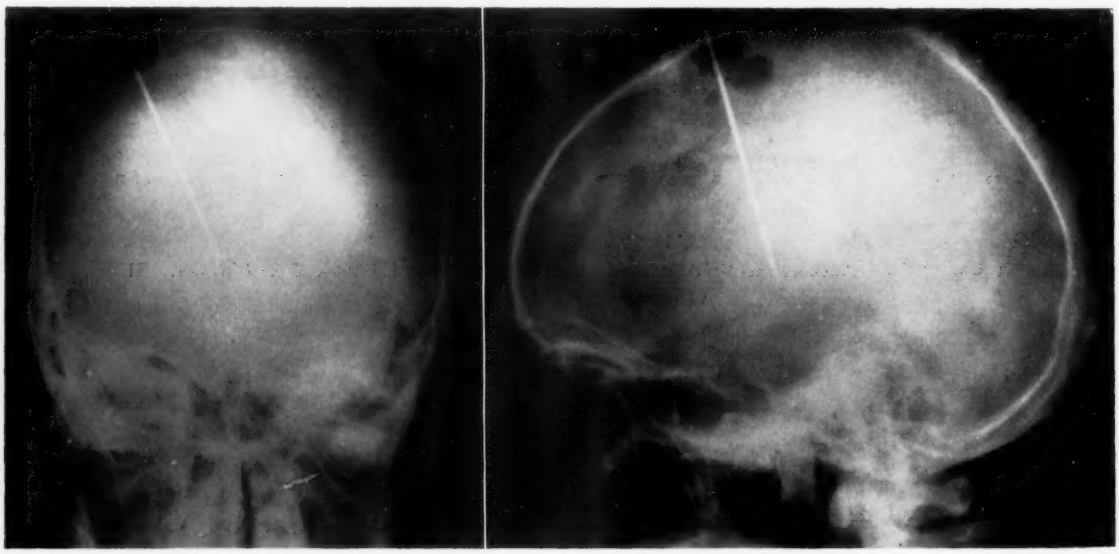

Fig. 7. Roentgenogram of needle in position. The small isotope is scarcely visible beyond and a little to one side of the tip of the needle.

DISCUSSION

Palladium 109 has now been employed in this manner in the treatment of 8 patients, in 2 of whom the insertion was bilateral. The use of fluoroscopic guidance eliminates the complexities of stereotaxic instruments, most of which require rigid fixation to the bony skull to be of value. Its superiority over serial roentgenograms lies mainly in the elimination of the delay that processing of these requires. The special needle makes multiple empirical punctures unnecessary. The beta source provides a very accurately controlled lesion. Its small size and gradual development over forty-five to ninety minutes are both factors of safety. If a single lesion proves too small, it can be easily enlarged at a later date. The short half life of palladium 109 and virtual freedom from gamma radiation make handling a simple process. This short half life of 13.5 hours is, however, a significant disadvantage in that hospitals some distance away from a nuclear reactor cannot be supplied. Sr^{90} in a perfectly sealed container could be used but the possibility of accidental breakage would be a real problem with this isotope of twenty-eight years half life. Ag^{111} of half life 7.5 days is now under investigation and may prove to be a better beta source. It has been used in the treatment of 2 patients (bilaterally).

SUMMARY

1. The ideal method of creating deep cerebral lesions should be safe, simple, and under rigid control at all times. The lesion should develop slowly so that any undesired change can be detected and arrested at the earliest possible stage.

2. Palladium 109 in the form of a metallic wire 3 mm. long, weighing 2.8 mg. and with an activity of 20 mc produces in brain a necrotic lesion of 5–6 mm. diameter. It is first visible after forty-five minutes application and reaches its maximum size after ninety minutes.

3. With the aid of fluoroscopic image intensifiers and a special needle, this convenient metallic source (Pd^{109}) can be accurately placed in deep cerebral tissues under local anesthesia. The fluoroscopic radiation to which the patient is exposed approximates that of a gastrointestinal examination.

4. Satisfactory alleviation of the tremor and rigidity of Parkinson's disease has been achieved by this method.

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A CRITICAL EVALUATION OF EXTERNAL BODY SURFACE COUNTING IN THE DETERMINATION OF CARDIAC OUTPUT WITH RADIOACTIVE ISOTOPES*

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A USEFUL estimate of cardiac output can be obtained, using either the Fick principle of gas exchange or the Hamilton-Stewart method[4,5,6,8,24,25,26] of dye dilution. These techniques have found limited clinical use, however, because of their technical complexities and of the need for frequent sampling of arterial blood. Prinzmetal and co-workers[18,19] in 1948 proposed that a gamma-emitting isotope be used as the indicator for the Hamilton-Stewart dilution technique, and that the concentration of the indicator be measured externally by placing a radiation detector over the precordium. If this modification were to yield accurate data, it would be an ideal clinical test, taking only minutes to perform, and requiring only a single peripheral venous sample. It is the purpose of this paper, however, to present data demonstrating such great errors as to negate the usefulness of this technique, even for comparative purposes.

EXPERIMENTAL INVESTIGATIONS

Three accepted variants of the Hamilton-Stewart technique were utilized to obtain control values of the cardiac output. These three different methods were cross-checked a number of times, found adequate, and therefore used interchangeably. In all cases, the indicator (either Evans blue or radioiodinated albumin) was injected intravenously as a discrete bolus of small volume (0.2–1.0 ml.) in a short time interval. The dose of I^{131}-albumin varied from 12 to 120 μc in patients, and from 8 to 30 μc in dogs. The basic method consisted of collecting serial arterial blood samples in test tubes taped to a revolving kymograph drum, analyzing each sample for concentration of indicator, and plotting the time-concentration curve as a series of distinct points. A second method, using radioiodinated albumin, consisted of passing blood from the femoral artery through plastic tubing (Transflex) in a standard deep well scintillation counter and back to the femoral vein. The continuously changing radioactivity present within the well of the scintillation counter was measured with a rate meter and recorded on a linear recorder. In the third method, using Evans blue as the indicator, the varying concentration in the peripheral arterial blood was measured continuously with a couvette oximeter, the blood flowing from the artery through the instrument and then being discarded.[15] For each of the latter two continuous recording techniques, calibration was achieved by subsequently passing a known concentration of the indicator through the system under identical conditions. In each of these three techniques, the cardiac output (C.O.) equals Dose/Area (Fig. 1).

$$\text{C.O.} = \frac{\text{Dose } (\mu c)}{\text{Area } (\mu c \times \text{sec./ml.})}$$

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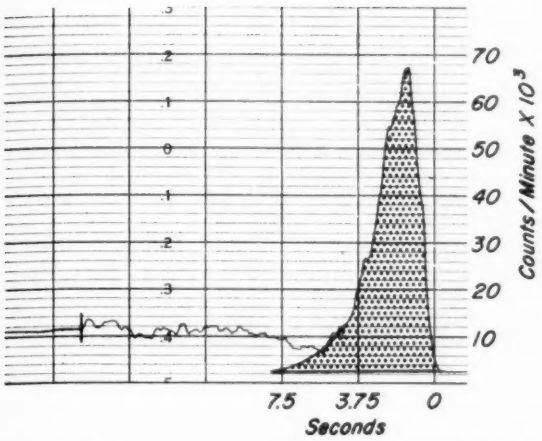

Fig. 1. Relative concentration of iodinated albumin recorded as blood flowed from the femoral artery through plastic tubing coiled in a deep well scintillation counter and back to the femoral vein (Dog #22).

For the precordial determinations, a scintillation detector was placed over the anterior chest wall, the precise area overlying both ventricles having been previously selected by fluoroscopy. The counting rate was again measured by means of a rate meter and recorded on a linear recorder. Since a laboratory standard cannot be introduced into this system, the curve must be calibrated by measuring the final counting rate after complete mixing of the isotope throughout the blood volume. The position of the detector remained unchanged during this five or ten minute period. At the time of the final reading, a venous blood sample was taken and analyzed for the final concentration of the circulating indicator. Thus, the area under the initial curve and the final concentration were obtained in relative units, and the absolute concentration was obtained from the withdrawn blood sample. In this instance,

$$\text{C.O.} = \frac{C_f \times \text{Dose}}{\text{Area} \times \text{Conc. Venous Blood}} \text{ (Fig. 2)},$$

where C.O. = Cardiac Output (ml./sec.)

C_f = Counts/second

Area = Counts/second × seconds

Conc. Venous Blood = μc/ml.

The rate meter was operated in all cases with a time constant of 0.5 seconds during the initial phase and of 2.5 seconds during the equilibration phase. The linear recorder moved at 12 inches per minute. The area under the curve was usually measured with a planimeter. Initially, the apparent cardiac output was determined on dogs using an uncollimated precordial detector and this was compared to simultaneous control values. A scintillation detector (SC-2A Nuclear Research) was utilized for counting. This employed a thallium activated sodium iodide crystal 1 square inch in size and housed in an aluminum can of 1 mm. wall thickness. Lead shielding was added circumferentially amounting to 19 mm. Anesthetized dogs were immobilized on a rigid frame. In Experiment 1 the detector was placed directly over the precordium locating the crystal itself within several millimeters of the skin surface. In some

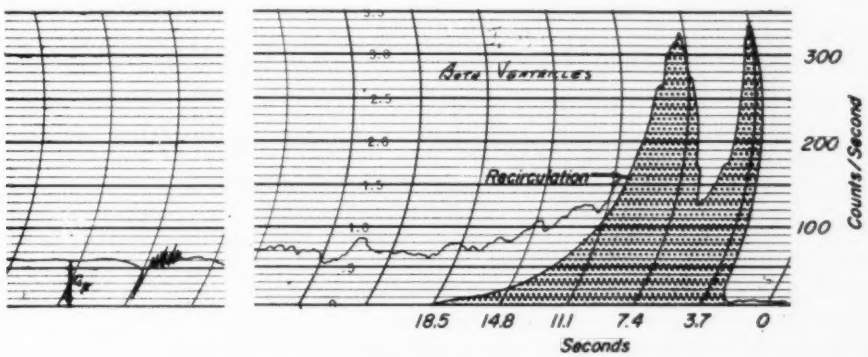

Fig. 2. Relative concentration of iodinated albumin recorded with a scintillation counter placed over the heart (open chest, Dog #11). A collimator was used with an aperture of 2.7 cm.

TABLE I

PRECORDIAL METHOD WITHOUT COLLIMATOR COMPARED TO SIMULTANEOUS CONTROLS (PERIPHERAL ARTERIAL METHOD)

Dog	Precordial (L/min.)	Control (L/min.)	Ratio
1	4.6	2.5	1.8
	4.2	3.1	1.4
4	2.1	1.1	1.9
5	2.2	1.5	1.5
6	4.2	3.0	1.4
7	2.3	1.6	1.4
8*	4.8	0.9	5.3
10	2.0	1.5	1.3
	2.1	1.4	1.5
	1.4	1.0	1.4
11 (open chest)	2.7	1.5	1.8
(open chest)	2.1	1.5	1.4
12	8.5	4.5	1.9
	11.0	5.4	2.0
	10.6	5.8	1.8
20	3.0	1.8	1.7
21	2.1	2.0	1.05
	3.2	2.9	1.1
		Average (see text)	1.8*

* Excluding Dog 8, average = 1.5.

cases, the detector was held directly above the exposed heart. Several dogs had two or three successive determinations performed using increasing doses of isotope so that the residual counting rate from one determination was a negligible portion of the counting rate of the following determination.

Table I presents the individual comparisons as well as the average of the ratios, indicating that the precordial method yields a value which tends to be one and one-half times the control.

Experiment II was performed under the same conditions as was Experiment I, except that a collimator having an aperture of 2.7 cm., a depth of 4 cm., and a wall thickness of 2.9 cm. of lead was placed over the crystal detector for precordial counting. The precordial determinations tend to approach those of the controls, although there is considerable variation of individual readings (Table II).

Experiment III was again similar, using a collimator with one of two possible apertures, but with the detector in various positions over the precordium. The shape of the curve obtained in a normal dog changed with each new position as shown in Figure 3. In all cases the first peak represents the isotope passing through the right heart, and the second through the left heart. In Table III are listed the varying cardiac output

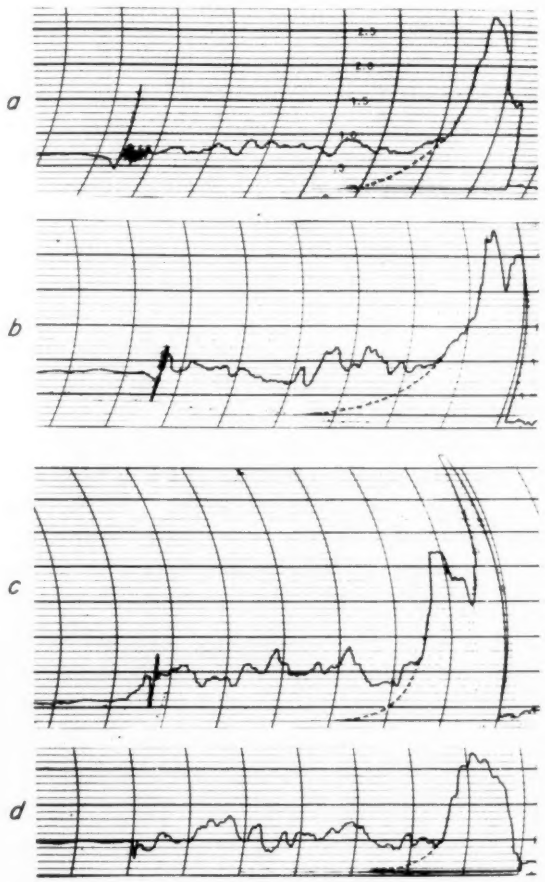

FIG. 3. Successive precordial recordings with various positions of the scintillation counter over the precordium (Dog #19, collimator used with aperture of 2.7 cm.). (*a*) Near cardiac apex; (*b*) 2 to cm. right; (*c*) 2 cm. cephalad; (*d*) 5 cm. caudad.

Table II

PRECORDIAL METHOD WITH COLLIMATOR (APERTURE OF 2.7 CM.) COMPARED TO SIMULTANEOUS CONTROLS (PERIPHERAL ARTERIAL METHOD)

Dog	Precordial (L/min.)	Control (L/min.)	Ratio
13	1.8	1.7	1.1
	1.6	1.5	1.1
	0.8	1.6	0.5
	1.4	1.6	0.9
	1.4	1.6	0.9
	1.4	1.8	0.8
21	2.0	2.1	1.0
	2.4	2.4	1.0
11 (open chest)	2.4	2.6	0.9
15	2.5	1.9	1.3
19	3.7	2.1	1.8
20	2.4	2.0	1.2
12	9.2	6.2	1.5
	8.4	6.0	1.4
	9.5	6.1	1.6

determinations. Slight differences in positioning alone may cause the apparent output to range up to twice the control value.

Experiment IV was conducted in a similar manner with the distance from the detector to the skin surface altered between the successive readings. The precordial detector was either uncollimated or was collimated to an aperture of 2.7 cm. The results are presented in Table IV. Since several of these determinations were done without simultaneous controls, no definite conclusions can be drawn. However, the findings suggest that variations in distance also influence the apparent cardiac output.

DISCUSSION

The Hamilton-Stewart technique for determining cardiac output by analysis of the arterial time-concentration curve following intravenous injection of a bolus of an indicator substance has been demonstrated to be accurate, both mathematically and experimentally.[3,13–17,28,29] The cardiac output is inversely proportional to the area under the curve of concentration repres-

Table III

PRECORDIAL METHOD WITH CHANGING POSITION OF DETECTOR COMPARED TO SIMULTANEOUS CONTROLS

Dog	Precordial (L/min.)	Control (L/min.)	Ratio	Position of Counter	Aperture of Collimator (cm.)
19	3.7	2.1	1.8	Near cardiac apex	2.7
	3.2	2.6	1.2	To right of midline	2.7
	3.9	2.0	2.0	5 cm. caudad	2.7
	2.7	2.1	1.3	5 cm. cephalad	2.7
	2.3	2.1	1.1	4 cm. caudad	2.7
20	2.4	2.0	1.2	Near cardiac apex	2.7
	2.7	2.0	1.4	2 cm. to right	2.7
	2.4	1.8	1.3	2 cm. cephalad, slightly to left of midline	2.7
	1.8	1.9	0.9	2 cm. cephalad, slightly to left of midline	2.0
	2.1	1.8	1.2	2 cm. caudad, slightly to left of midline	2.0
	3.1	1.9	1.6	2 cm. caudad, in midline	2.0
	2.1	1.8	1.2	1.5 cm. cephalad, in midline	2.0
21	2.4	2.4	1.0	2 cm. cephalad to cardiac apex	2.7
	2.3	2.3	1.0	2 cm. to left	2.7
	2.2	2.3	1.0	2 cm. caudad	2.7
	2.2	2.1	1.0	2 cm. caudad	2.0
	2.3	1.5	1.5	Just to right of midline and just above cardiac apex	2.0
	0.9	0.9	1.0	1 cm. caudad, in midline	2.0

TABLE IV

PRECORDIAL METHOD WITH CHANGING DISTANCE BETWEEN DETECTOR AND HEART

Subject	Precordial (L/min.)	Control (L/min.)	Ratio	Position of Detector	Aperture Size of Collimator (cm.)
A.W.	8.6			Against chest	No collimation
	7.8			Raised 1½ inches	No collimation
	7.6			Against chest, moved to right	No collimation
B.G.	14.6			Against chest	2.7
	12.8			Raised 1 inch	2.7
	11.4			Raised 2 inches	2.7
P.T.	7.4			Against chest	2.7
	8.8			Raised 1½ inches	2.7
C.D.	15.3			Against chest	2.7
	7.6			Raised 1½ inches	2.7
Dog 22	2.0	2.1	1.0	Against chest	2.7
	1.7	2.2	0.8	Raised 1 inch	2.7
	1.9	2.2	0.9	Raised 2 inches	2.7
	2.0	1.8	1.1	Raised 3 inches	2.7
Dog 14	2.9			Against chest	2.7
	6.4			Raised 3 inches	2.7
Dog 6	4.2	3.0	1.4	Against chest	No collimation
	4.0	3.0	1.3	Raised 2 inches	No collimation
Dog 7	2.3	1.6	1.4	Against chest	No collimation
	2.7	2.0	1.3	Raised 2 inches	No collimation
Dog 8	4.8	0.9	5.0	Against chest	No collimation
	6.0			Raised 3 inches	No collimation
Dog 15	2.5	1.9	1.3	Against chest	2.7
	2.4	1.8	1.3	Raised 1½ inches	2.7
Dog 16	2.0			Against chest	2.7
	2.3	2.1	1.1	Raised 1 inch	2.7

enting the first circulation of the isotope past a given point of measurement. For the calculated value of cardiac output to be valid, it is necessary that the area under the curve be that of the first circulation only. Recirculated blood appears before the primary curve is completed, necessitating extrapolation of the primary downstroke. Since the downstroke closely approximates an exponential disappearance, this extrapolation is separately accomplished after plotting the downstroke on semilogarithmic paper. The extrapolated portion is in turn replotted on the original tracing to outline the entire area of the primary curve.

The availability of gamma-emitting isotopes has stimulated efforts to develop external counting techniques to obtain this time-concentration curve within a peripheral artery or within the heart.[1,2,7,9–12,20–23,27,31] If valid, this major technical simplification would permit this to be a routine clinical laboratory test. The inability to selectively analyze for the concentration within a known arterial segment, however, makes the external counting method inherently unreliable, as illustrated by the following two examples. In

one extreme, if an artery and vein lie side by side, with equal lumen, and equally within the "sight" of the detector, then the "final concentration" will be exactly twice that of the true arterial concentration which should be used. This will then yield an apparent cardiac output exactly twice the true value. This would be acceptable if it could be established that equal quantities of arterial and venous blood were always being seen, but, as this in turn is not necessarily true, uncertainty is inevitable. The inability to selectively "see" a circumscribed volume is even more pronounced with the precordial technique. Even with heavy collimation, a cone with increasing penumbra forms the contributing volume, which must include portions of the anterior and posterior chest wall as well as cardiac, pulmonary, and great vessel blood. The total contribution of counts from each of these sources is a function of area seen (increasing as a power function of the distance), of intervening tissue (decreasing as an exponential function), and of scatter (increasing unpredictably). The distance of the detector from cardiac or aortic blood is both unpredictable and uncontrollable. As a second extreme, if the detector is placed sufficiently far from the heart (across the room), the entire body will be seen. No major change in counting rate will be observed after the isotope has been injected, and the mathematical absurdity will result that the cardiac output is infinite. The specificity, and therefore the accuracy, of the precordial technique lies between that achieved when arterial blood is passed within the counter and this latter extreme yielding an answer of infinity.

Both of these arguments are illustrated by the experiments described above. The precordial techniques consistently yielded high values, more so with lesser collimation.

That these values were not exactly twice the correct values also would be expected because arterial blood predominates within the volume of the chest "seen." The influence of distance on further reducing the dependability has been demonstrated. The effect of respiration was investigated in several subjects by noting the change in the final equilibration level between deep inspiration and expiration (without the Valsalva effect). The greatest variation observed was 30 per cent. In one instance, the subject moved her back slightly; a doubling of the final equilibration value resulted from the slight change in position. Although good curves can be obtained from precordial counting, the descending limb is invariably more difficult to define than with curves obtained from isolated arterial blood. This is due in part to the more rapid appearance of recirculated blood. One or more extra peaks are frequently observed in the precordial tracing, due perhaps to coronary artery or to bronchial artery recirculation.[28] The inclusion or exclusion of the area beneath these peaks will influence the apparent cardiac output by as much as 30 per cent (Fig. 4). Fifteen other curves were checked in a similar manner resulting in an average variation of 10 per cent (Table v).

Several technical points warrant mentioning. I^{131} tagged to albumin was chosen as the indicator in preference to free radioiodide, since it has been found that as much as 30 per cent of the ionic isotope leaves the circulation during its first passage.[30] The radioiodinated albumin solution should be diluted with albumin water for the injection or with a detergent for the standard, since albumin tends to "plate out" on the walls of the container. The instrumentation should be checked to make sure that the

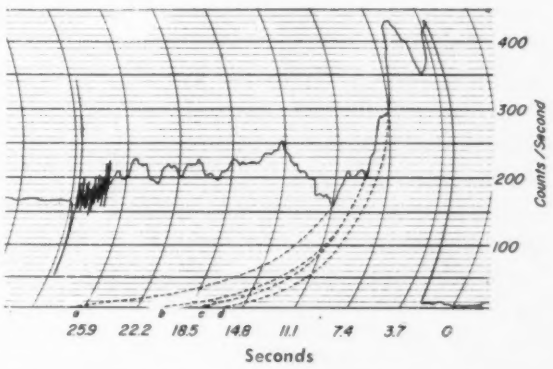

Fig. 4. Precordial curve demonstrating extra peaks on downstroke. (Dog. #17). C.O. = (*a*) 2.9 L/min.; (*b*) 3.5 L/min.; (*c*) 3.6 L/min.; (*d*) 3.9 L/min.

TABLE V

VARIATION IN THE APPARENT CARDIAC OUTPUT WITH DIFFERENT INTERPRETATION OF THE DOWN STROKE (SEE FIG. 4)

Extra Peak Included (L/min.)	Extra Peak Omitted from Area (L/min.)
14.6	15.4
2.0	2.2
1.9	2.0
1.7	1.8
3.6	3.9
3.7	3.9
3.0	3.5
2.4	2.6
2.7	2.9
1.8	2.0
2.2	2.5
2.1	2.4
2.1	2.9
2.4	2.6
2.2	2.4

response is linear, and to ascertain the rate and extent of zero drift, since zero drift tends to occur with most count rate meters and varies with different time constants. Since the final equilibration counting rate is considerably less than the peak counting rate, a small error introduced by zero drift may well represent a large proportion of the final equilibration counting rate, which will yield an error in the final calculated cardiac output in direct proportion to its relative magnitude. A reasonably short time constant (0.5 sec.) is necessary during the initial phase after injection to accurately record the rapidly changing counting rate encountered. In one published paper, it was obvious from inspection that the downstroke shown and analyzed represented the discharge of the instrument with a relatively long time constant, rather than the decreasing isotope concentration in the blood stream.

The use of a "focusing" collimator has been proposed to permit analysis of concentration within a selected volume. This attachment is useful for determining variable concentration across a plane at the focal distance, if there is little or no activity proximal or distal to the plane of interest. However, a larger cross-section is "seen" in planes both proximal and distal, and activity proximal will contribute excessively to the counting rate because of the inverse square as well as the area functions. This obvious theoretical analysis has been confirmed experimentally with phantoms in this laboratory.

In Figure 3 are shown the curves obtained from a single dog, varying only the position of the counter. They are reproduced here, partly to demonstrate that the position chosen affects the calculated apparent cardiac output, and partly to illustrate the uncertainty which attends the interpretation of such curves in terms of functional or anatomic cardiac abnormalities.

SUMMARY

The precordial external counting technique for the determination of cardiac output, while clinically desirable, is in fact unsound. Experimental data are presented to confirm this.

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CARCINOMA OF THE TONSILLAR AREA: FACTORS INFLUENCING THE RESULTS OF TREATMENT*

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INTEREST in the results of treatment of carcinoma of the tonsillar area developed at the Columbia-Presbyterian Medical Center because it was our impression that patients with this disease responded favorably to radiation therapy. An analysis of such patients treated during the past twenty-five years is reported here.

In terms of incidence, carcinoma of the tonsil is not a problem of great magnitude, comprising about 1.5–3 per cent of all cancers. In the United States cancers of the oral cavity and pharynx occur in a fairly uniform pattern, with malignant tumors of the tonsil and pillars accounting for about 10 per cent of all cancers of the upper air passages, second to cancer of the larynx in frequency. In general, there are four epitheliomas for every lymphosarcoma of the tonsil. Only the former are considered in this review.

Eighty-one of 88 patients with microscopically proved squamous cell epithelioma of the tonsillar area received at least one radiation treatment at this hospital. The 81 treated patients comprise our study group. The 7 untreated patients were referred to this hospital for diagnosis only. Our series was compared with those in the literature which are of similar composition and selection (Table 1). These series are comparable as to age, sex distribution, duration and extent of disease but represent a widely different pattern of management and diversity of opinion as to the preferable method of treatment. The unadjusted net five-year survival rate is used as a basis of comparison and the total group of patients in each series is comprised of those "exposed to the risk" of surviving a five-year period. The 6 patients in our group who were lost to follow-up before the end of a five-year period are considered dead with cancer.

I. INFLUENCE OF CLINICAL AND TECHNICAL FACTORS ON SURVIVAL

Techniques and Modern Drugs. It is clear from a comparison of the clinical results that the advances in technique of radiation therapy during the past twenty years have not resulted in any correspondingly large increase in the proportion of patients cured. The use of new drugs has reduced the number of patients dying from pneumonia and other infections, while better methods of dosage measurement and control have reduced the incidence of radiation injuries, but the calculation of chi square and similar statistical tests casts doubt upon the significance of differences in survival rates among the series shown in Table 1. This statistical method is appropriate here since practically all cases of carcinoma of the tonsil have been treated by irradiation only.

Of the 81 patients, the primary treatment was roentgen therapy alone in 62, roentgen therapy combined with interstitial radium in 9, and roentgen therapy and radical neck dissection in 8 patients. Surgery alone was the selected treatment for 2 patients, with neither surviving for five years. There were 17 five-year survivals in the group of 62 patients, and 2 five-year survivals in the other two groups.

A plot of total tumor dose and duration of radiation therapy in our survivor and nonsurvivor groups fails to show a simple

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TABLE I

Author	Period	Died	Survived	Total	Per Cent Survived Five Years
Presbyterian Hosp.	(1930–1958)	44	21	65	32
Parshall and Stenstrom[15]	(1926–1950)	57	15	72	21
Walker and Schulz[18]	(1936–1945)	33	6	39	15
Paterson	(1940–1944)	46	6	52	12
Berven	(1923–)	67	11	78	14
Wood and Aird[21]	(1934–1945)	57	23	80	29
Cade and Ledlie		65	17	82	21
Ennuyer and Bataini[5]	(1919–1947)	330	70	400	17.5
Coutard[2]	(1920–1926)	27	6	33	18
Martin and Sugarbaker[14]	(1930–1935)	88	19	107	18
Duffy[4]	(1921–1928)	39	10	49	20
				1,057	19.3
	$\tilde{x}^2 = 13.79$				
	D = 10				
	P = 0.18				

Collected series including Presbyterian Hospital group showing the five-year survival in each. The over-all five-year survival is 19.3 per cent in 1,057 cases. The five-year survival at Presbyterian Hospital is 32 per cent. The probability of the differences in the five-year survival rates in the groups shown being due to chance alone is 18 per cent, hence the difference between the Presbyterian Hospital group five-year survival of 32 per cent and the average five-year survival of 19.3 per cent is not significant.

relation between dose and duration of treatment and result (Fig. 1). Excluding the 7 nonsurvivors who received a dose of less than 1,500 r, we see that the final outcome cannot be predicted from the dose or the duration of treatment. Of particular interest is the group of patients who received between 3,000 and 4,000 r tumor dose in three to five weeks. In 2 of 5 patients so treated a five-year survival resulted.

Presenting Symptoms and Extent of Disease. The result of treatment does not seem to be affected by the type of initial symptom (Table II). As might be expected,

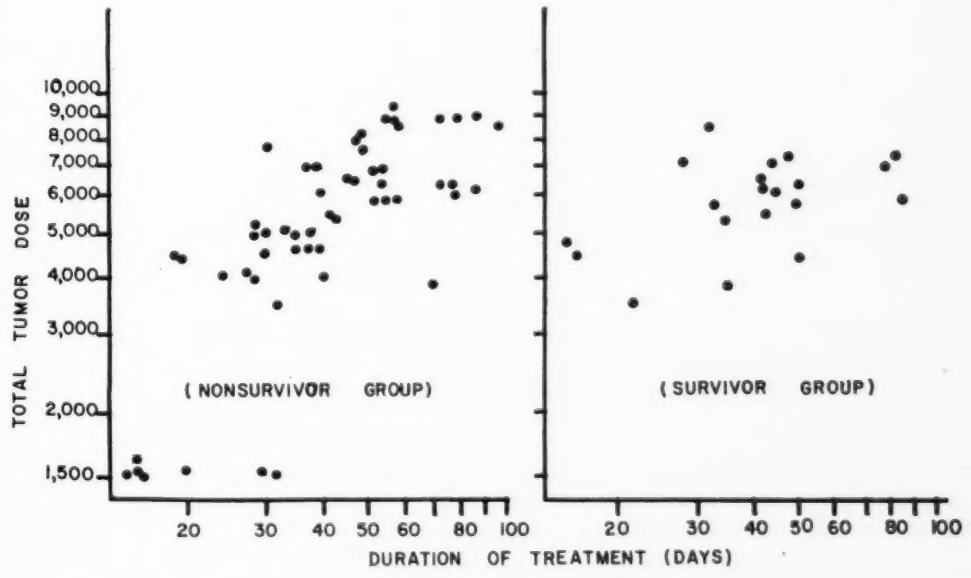

FIG. 1. Total tumor dose and treatment time in survivor and nonsurvivor groups. No correlation between tumor dose and survival is apparent.

TABLE II

Symptom	Frequency	
	Total (per cent)	Survivor (per cent)
Sore Throat	73	70
Neck Mass	25	28
Dysphagia	18	19
Oral Mass	11	10
Trismus	7	9
Bleeding	4	5
Duration	4.5 Mo.—(mean)—4.5 Mo.	

Symptoms on admission in order of frequency. The presenting symptoms offer no prognostic aid, being similar in the survivor and nonsurvivor groups.

symptomatology depends largely on the gross features of the tumor. The lesion may arise in a crypt and present only a small portion on the surface. As it enlarges the tumor usually tends to fungate and erode the surface of the tonsil. By the time the lesion has reached a diameter of about 2 cm., beginning invasion of the neighboring structures takes place in about the following order: the tonsillar pillars, the soft palate, the base of the tongue, the pharyngeal walls, the alveolar ridges and the mucosa of the cheek. The tactile sense of the pharynx is slight in comparison with that of the oral cavity itself, accounting for the insidious onset of symptoms and the fact that only 10 per cent of the patients state that they first became aware of a lump in the throat (despite an average tumor size of 3.5–4 cm. diameter). In contrast to the minor nature of the oral symptoms, awareness of a mass in the neck was the first symptom in 25 per cent of the patients. However, 70 per cent of the group had clinical evidence of cervical lymph node metastases when first seen. The subdigastric lymph node was the first node involved in all cases, and later the disease progressed down the jugular chain to the clavicle and often into the posterior triangle of the neck along the accessory chain. Lymphadenopathy was bilateral in 15 per cent of the cases.

The duration of symptoms is not very important as a guide to the final result, but the prognosis is usually poor when lymphadenopathy has been present for more than one year. The median duration of life of those with lymph node metastases (eleven months) and those without palpable lymph nodes (fourteen months) is not markedly different (Fig. 2). Of the patients who died with cancer, the majority of those who had no lymph node involvement when treated died without cancer in the lymph nodes, while the majority of those in whom metastases were present at the time of treatment had cancer both at the primary site and in the lymph nodes at the time of death.

To compare the radiosensitivity of the primary lesion and the lymph node metastases from data in the patients' records is difficult. This is because accurate treatment planning in all patients with designation of the dosages has only been routine in our hospital for ten years. However, from inspection of the older records, it is doubtful that the dose in the lymph nodes was as high as the dose to the primary lesion in most instances. Despite this, the primary tumor and the lymph node metastases behaved in the same way in the majority of cases. They decreased in size and persisted or recurred together. Furthermore, our experience conforms to that of other

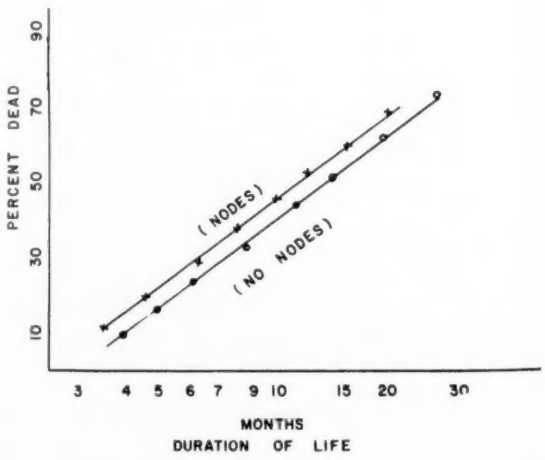

FIG. 2. In the nonsurvivor group survival is independent of the presence or absence of clinically positive cervical lymph nodes on admission.

authors in that tumor size and presence or absence of invasion of the tongue or soft palate or both have little influence on the five-year survival results of radiation therapy.

Histology. The histology of the lesions of this group of cases falls into three categories: well differentiated squamous cell carcinomas, moderately well differentiated to moderately undifferentiated, and completely undifferentiated carcinomas. About half of the group had moderately differentiated to moderately undifferentiated lesions. In comparing the survival rates in the three groups, they are found to be essentially the same, indicating that the degree of pathologic differentiation has no influence on the survival of the individual.

Sex, Age and Economic Status. Our experience with 81 treated patients is shown in Figure 3 according to the year of treatment and the duration of life or follow-up study. The female patients are marked by a symbol. As in oral cancer, in general, carcinoma of the tonsil is seen most often in males, with 75–90 per cent males in reported groups. There has been an increase in the relative incidence among women in recent years. The five-year survival rate of patients in the series treated prior to 1943 and after 1943 is identical, based on the fact that although there are more women in the more recently treated group and their survival rate is higher, the males in the group after 1943 survived for a shorter period of time than previous to 1943.

The average age group for women developing malignancy of the tonsil as shown in Figure 4 occurs about five years earlier than for men. The survivors are fairly evenly distributed according to age, and age at onset of treatment is of little value in predicting the outcome. The five-year results are presented in Table III to illustrate the marked and highly significant difference in survival in women and men. The results are expressed by the actuarial method as the probability of a patient with carcinoma of the tonsil surviving five years, and in the less accurate but more familiar unadjusted net survival rate (where we have assumed that all patients lost to

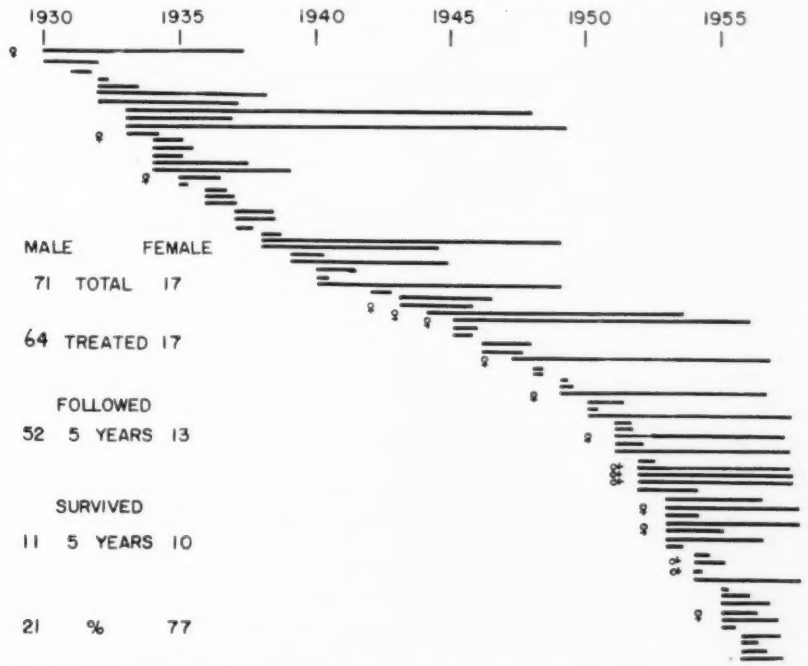

FIG. 3. Survival in 64 treated males and 17 treated females. The lines representing the 17 females are indicated. Fifty-two males and 13 females were followed for five years. Female survival 77 per cent; male survival 21 per cent.

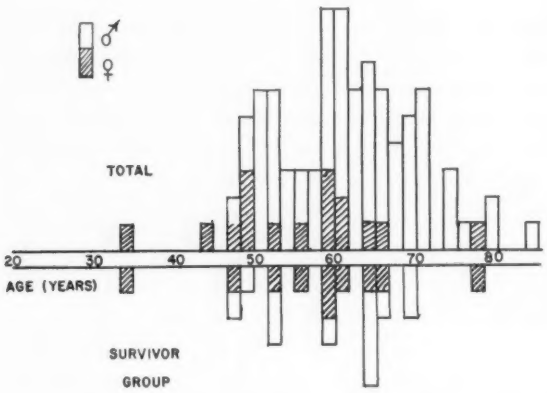

FIG. 4. Age of onset of carcinoma of the tonsillar area in males and females. Incidence is greatest in the sixth to eighth decades. Males outnumber females 71 to 17.

follow-up are dead with cancer). This sex difference in survival rate has been noted by authors in France, England and the United States. No significant difference in treatment results has been noted between private and clinic patients.

II. RECURRENCES

Almost one-half of our patients had complete regression of the primary lesion and lymph node metastases after radiation therapy, one-fourth had a partial response, and one-fourth showed no significant response. Of the 35 patients who had complete regression of their lesion, 25 received tumor doses of at least 5,000 r in five weeks and 17 of 35 patients received tumor doses of more than 6,000 r in six to seven weeks. However, there were 46 recurrences in 42 patients, 4 of the patients having more than one recurrence. The primary oral lesion recurred more frequently than the lymph node metastases.

The incidence of recurrence was similar in men and women. The majority occurred within the first year. Most patients with recurrence within the first twelve months after irradiation were not benefited by further treatment. When recurrence did not appear until after one year, supplemental treatment appeared to be of definite value. In our group of patients, definitely distinct second oral lesions occurred in 4 men and 3 women. Distant metastases contributed to the death of 6 per cent of the patients, the metastatic sites including the lungs, brain, abdominal viscera, and skeleton.

DISCUSSION

When we look in the conventional places for aids in predicting the success or failure of radiation therapy, we find little to assist us. It would seem reasonable to conclude we are ignorant of the factor or factors which have the greatest influence on the final prognosis. We have seen that techniques and modern drugs, presenting symptoms and extent of disease, histology, and the age and economic status of the patient are not the important factors. The only clue that we have is the remarkably high survival rate in women.

When patients are studied who have sur-

TABLE III

Author	Group	No.	Five-Year Survival Rate			
			Actuarial Method	σ_P	No.	Net Survival
Presbyterian Hosp.	Total	81	34%	5.6	65	32%
	Male	64	28%	5.9	52	21%
	Female	17	63%	12.1	13	77%
			$P_1-P_2/\sigma_{P_1-P_2}=>2.5$			$x^2=13.6$ P = < .0005
Wood and Boag[20]	Total	80	35%		51	33%

The survival of the total treated group of 81 patients observed for one week or more, calculated by the actuarial method, is 34 per cent at five years. The unadjusted net survival rate of the 65 patients observed for five years or more is 32 per cent. The percentage survival rates by sex, handled in the same manner, is indicated.

TABLE IV

FIVE-YEAR SURVIVAL GROUP

Patient	Age	Sex	Lymph Node Metastases	Recurrence	Second Primary Oral Carcinoma	Dead with Cancer	Dead without Cancer	Alive with Cancer	Alive without Cancer
H	51	M	x						x
W	63	M	x				x		
V	59	M	x	x		x			
T	62	M	x	xx		x			
E	50	M		xx				x	
S	66	M	x						x
L	46	M		x		x			
H	62	M	x	x					x
R	49	M	x						x
M	70	M	x				x		
W	61	M	x	x			x		
B	38	F							x
F	66	F	x						x
C	52	F	x	xx		x			
B	54	F	x	x					x
C	70	F					x		
L	59	F							x
S	46	F	x	x	x				x
R	64	F	x	x				x	
D	58	F	x	x	x	x			
C	60	F		x		x			
Total 21 patients			15	15	2	6	4	2	9

Eleven males and 10 females survived five years. There were 8 recurrences in 6 of the males and 7 recurrences in 6 of the females. Second primary neoplasms occurred in 2 of the females. Three of the males and 3 of the females died with cancer after surviving for five years. One male and one female are alive with cancer. Thirteen individuals are alive free of disease at five years or longer.

vived five years or more (Table IV), we find that the majority have not remained free of their disease: there were 15 recurrences in 21 patients, symptomatic tumor was present in 6 patients at death, and 2 patients are alive with symptoms due to tonsillar cancer. A second oral carcinoma occurred in 2 patients.

There is no evidence that the form which the radiation therapy of the primary lesion takes (radium alone, radium and roentgen ray, orthovoltage or supervoltage external therapy alone) has an important effect on the outcome. The method of management of cervical lymph node metastases has been more difficult to decide. In view of the fact that only 8 per cent of those patients who had no palpable metastases at the time of the first examination later showed cervical lymph node involvement, prophylactic neck dissection is considered illogical and unnecessary by some. Martin[12] of Memorial Hospital, New York City, feels that treatment is not delayed unnecessarily if patients are followed closely for the subsequent appearance of cervical lymph node metastases. In the 8 patients who underwent radical neck dissection in our group, 4 had recurrence and 2 patients survived five years.

The treatment plan utilized by Wood and her co-workers[20,21] delivered doses to the cervical lymph node metastases which approached those delivered to the primary tumor. They found as many cases in which the metastases responded more rapidly than the original lesions as the number of instances in which the primary tumor responded more rapidly than the lymph node metastases. The five-year survival of 35 per cent in their series[21] in spite of careful attention to technique led them to conclude that it was no longer possible to ascribe all failures in radiation therapy to inadequate dosage alone, and that further improvements in the distribution and control of dosage are not the most important factors which must be considered in the future application of radiation to this region. From an analysis of our material we must concur.

The degree of differentiation in the pretreatment biopsy specimen has been found to be of no significance as a guide to prognosis for the particular patient being treated. The difference in survival rate between males and females suggests that here may be a factor worth investigating. The increased incidence of carcinoma of the tonsillar area in women in recent years may be related to their increased tobacco and alcohol consumption, the only factors which are known to be of possible etiologic importance.[22]

It is apparent that we have not found a satisfactory prognostic aid thus far in our study of the problem of carcinoma of the tonsil. Without a reliable method of predicting the outcome or of selecting the most hopeful treatment for the individual patient, our five-year survival figure is 32 per cent. Perhaps this figure can be improved when we better understand the biologic response of this tumor to radiation. The one significant and suggestive lead we have is a marked difference in response and survival in females and further study of this factor may yield benefits.

SUMMARY

1. Eighty-eight patients with microscopically proved squamous cell carcinoma of the tonsillar area were seen at the Columbia-Presbyterian Medical Center from 1932–1957.

2. Eight-one patients were treated, 79 with radiation. Eight of the 79 had radical neck dissection.

3. Presenting symptoms, extent of disease, histology, age, modern techniques and drugs, and economic status did not influence survival.

4. Sex was the only factor which appeared to influence survival rate. This was significantly increased in females as compared with males. Seventy-seven per cent of females followed five years or more survived as compared with 21 per cent of male patients.

5. The net five-year survival rate for 81 patients with squamous cell carcinoma of the tonsillar area was 32 per cent.

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LYMPHOSARCOMA OF THE STOMACH

REVIEW AND CASE REPORTS

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LYMPHOSARCOMA arising as a primary neoplasm in the stomach is infrequent but when recognized and treated adequately has a better prognosis than carcinoma. This has been emphasized repeatedly in articles on lymphosarcoma of the stomach.[37,72,77] The purpose of this article is to review the literature on lymphosarcoma of the stomach and to report 13 new cases.

Lymphosarcoma is defined as a true malignant neoplasm arising in lymphoid tissue from proliferation of atypical lymphocytes.[24] The first recognition of lymphosarcoma as a disease entity is credited to Kundrat (1893).[76] Ewing[24] states that any group of lymph nodes or any lymphoid structure may be the primary site of lymphosarcoma.

INCIDENCE

Ackerman and del Regato[1] state that lymphosarcoma is often seen first as a generalized process, but an increasing number of cases is being reported with a definite focus of origin. They also state that lymphosarcoma frequently arises from the region of Waldeyer's ring and that the second most common location is in the gastrointestinal tract. Sugarbaker and Craver,[76] reviewing a series of 196 cases of lymphosarcoma in general, found that 5.5 per cent arose in the gastrointestinal tract. In the evaluation of 545 cases of malignant lymphoma by Gall and Mallory,[30] 13 per cent were found to produce gastrointestinal involvement. Shimkin and associates[70] reviewing 215 cases found that 8.3 per cent had primary sites in the digestive tract.

Neoplasms of the stomach are responsible for 12.2 per cent of the cancer deaths in the general population with an incidence of 26.4 per 100,000 population, based on the ten city survey in 1947 reported by Heller *et al.*[33] In the male population, if carcinoma of the skin is excluded, neoplasms of the stomach are exceeded in frequency only by carcinoma of the prostrate.[33]

Sarcoma has been reported to constitute approximately 1 per cent of the malignant lesions of the stomach.[24] Marshall and Meissner,[47] reviewing all gastric neoplasms seen at the Lahey Clinic over a twenty year period, found the incidence of sarcoma to be 3.5 per cent. Ochsner and Ochsner[53] recently reported that sarcomas accounted for 5.7 per cent of the malignant gastric neoplasms seen at the Ochsner Clinic. Lymphosarcoma is reported to comprise from 45 per cent to 60 per cent of the gastric sarcomas.[54]

Recently, more and more cases are being reported in the literature and it appears that the incidence of lymphosarcoma of the stomach is higher than formerly believed. Warren and Lulenski[81] noted a frequency of 2.5 per cent in 569 gastric neoplasms. Yarnis and Colp[85] observed 8 cases in 250 patients with neoplasms of the stomach, a frequency of 3.2 per cent. Wellman and Haines[83] found lymphosarcoma of the stomach accounting for 9.4 per cent of all gastric malignancies. Lame *et al.*[40] reported that malignant lymphomas comprised 20 per cent of their gastric neoplasms. In 1952, Snoddy[72] made an extensive review of the world's literature and reported 474 cases including 34 personal cases. Since that time there have been approximately 360 additional cases published. The present series contains 13 new cases of lymphosarcoma of the stomach.

According to the incidence of carcinoma in the general population one would expect the development of 39,600 new cases of

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carcinoma of the stomach in a total population of 150 million, based on the incidence rates found in 1947.[33] If one accepts the frequency of sarcoma as being 1 per cent of all gastric neoplasms[24] and that lymphosarcomas constitute 50 per cent of this group,[54] one would expect the development of approximately 200 new cases of lymphosarcoma of the stomach per year in the general population. It would appear that of these, many cases are presumably diagnosed as advanced inoperable carcinoma with no definite treatment given or if biopsy is performed are misinterpreted as anaplastic carcinoma.

AGE DISTRIBUTION

The age of cases reported ranges from three and one-half years to ninety-one years.[62] Madding and Walters[45] reported the average age of their 41 cases as 46.7 years. Snoddy[72] found that the average age was 46.5 years for a group of 267 (out of 467) reported cases including his 34 cases which had an average age of fifty-five years. A review of 298 cases of a total of approximately 360 reported since Snoddy's publication reveals an average age of 49.98 years. The average age of 13 cases in the present study is 57.7 years with a range of from twenty-seven to eighty-three years. This is still below the average age of sixty-one years for gastric carcinoma.[47] This trend toward a higher average age is probably a reflection of the increasing age of the total population.

SEX RATIO

The reported ratio of males to females ranges from equal involvement by Allen *et al.*[2] to 7:1 by Jenkinson *et al.*[36] In Snoddy's[72] analysis of 274 (out of 467) patients, males predominated 3.2 to 1. The ratio in 276 (out of the 360) of the recently reported cases was 1.74 to 1. In the present series of 13 cases there are 6 males and 7 females.

SYMPTOMATOLOGY

The various symptoms of gastric sarcoma offer little which is characteristic.[2,36,50,57] The duration of gastrointestinal symptoms varies from a few weeks to many years, and is frequently difficult to evaluate. In Snoddy's[72] cases, study of the history of symptoms ranged up to thirty years in duration, but he believes that symptoms lasting longer than two to four years are related to conditions other than lymphosarcoma. In 20 of his patients giving more specific information, the average duration of symptoms was six to eight months. In Wellman and Haines'[83] group of patients, the average duration of symptoms was 10.1 months with a range of two weeks to five years. In the present study symptoms ranged from two weeks to two years, with one patient reporting intermittent diarrhea for seven years.

Pain is the most common complaint, occurring as the initial symptom in more than 70 per cent of cases.[36,37] It may be generalized but more often it is localized in the midepigastrium, simulating peptic ulcer, although it is not always alleviated by eating.[52] Pain was one of the presenting symptoms in 10 of our 13 cases. The early occurrence of pain is apparently due to involvement of the submucosal plexus of nerves as pointed out by Madding and Walters.[45]

Anorexia and dyspepsia develop early and occur in the majority of cases. Nausea and vomiting may occur in 25 to 50 per cent of patients.[2,40] Hematemesis reported by Yarnis and Colp[85] to be unusual, occurs in 15 to 45 per cent.[2,72] Melena is observed in 20 to 30 per cent.[40] Both hematemesis and melena may be noted in approximately 15 per cent.[40] A few patients have reported prolonged and recurrent episodes of diarrhea consisting of 8 to 10 liquid stools daily.[83] The bowel movements are frequently related to the ingestion of food. There may be alternating periods of constipation and diarrhea. Prolonged unexplained intermittent diarrhea during the seven years before the diagnosis of lymphosarcoma of the stomach occurred in one case of the present series.

Weight loss is observed in 60 to 95 per

cent of patients, ranging from 4 to 79 pounds[17,40,72] with an average weight loss of approximately 15 to 22 pounds.[17,72] This is considered to be less than the average weight loss in patients with carcinoma of the stomach.[57,83]

Remitting fever is not regarded as characteristic of lymphosarcoma of the stomach, occurring most frequently in the generalized form with extensive involvement of lymph nodes.

If the total thickness of the stomach wall is involved, perforation may occur into the peritoneal cavity or into adjacent tissues. Snoddy[72] described acute perforation and peritonitis found at surgery in 2 out of his 34 personal cases. Berger *et al.*[7] noted perforation into the peritoneal cavity in 1 case and into retrogastric masses in 2 cases. Allen and associates[2] observed the perforation of a gastric lesion with the patient succumbing from this complication before surgical intervention. Crile *et al.*[17] also observed a case with spontaneous perforation. An acute perforation occurred in 1 case of the present study following mild left upper quadrant pain of two weeks' duration. At the time of surgery a 1×1 cm. perforation was present on the anterior surface of the stomach.

PHYSICAL EXAMINATION

The good general physical condition and the relatively younger age of these patients have been stressed repeatedly in the recent literature.[17,36,37,57] In the early cases there may be no positive physical findings.[2] In approximately 40 per cent epigastric tenderness or rigidity is the only finding. A palpable mass may be noted in 20 per cent[2] to 50 per cent[77] of cases. Four of the 13 cases in the present study had a palpable mass. In the more advanced cases the patient has lost considerable weight, appears anemic and may have fever. An abdominal mass and enlarged peripheral lymph nodes indicate a rather extensive disease process. In the more advanced cases it is frequently impossible to determine if the gastrointestinal involvement is secondary to a generalized lymphosarcoma or if the generalized process is due to extensive spread from a primary lesion arising within the gastrointestinal tract.[72]

LABORATORY FINDINGS

There is nothing characteristic in the blood picture to suggest lymphosarcoma of the stomach.[83] Jenkinson *et al.*[36] reported 2 cases having leukocyte counts of 14,000 with one patient having a relative lymphocytosis of 64 per cent. Six of 20 patients in Thorbjarnarson and co-workers'[79] series had lymphocytosis of 25 per cent or more, but this was not considered significant.

There may be a mild to moderate anemia in 50 to 65 per cent of the cases.[2] Only 10 to 15 per cent will have a red blood cell count below 3 million.[72] The average hemoglobin level is reported to be 9.8 to 10 gm.[36,79] Massive bleeding from the gastrointestinal tract resulting in melena occurs in 25[40] to 35 per cent.[17] Occult blood is found in the stools in approximately 66 per cent of patients.[2] Taylor[77] reported finding occult in all of his cases. Massive bleeding in the form of hematemesis and/or melena occurred in 3 cases while occult blood was found in the stool of 3 other cases in the present patient group.

The gastric analysis values differ from findings in carcinoma in that 65[17] to 75 per cent[2] of patients show free HCl. Wellman and Haines[83] reported finding normal amounts of free HCl in 7 patients with 1 patient demonstrating achlorhydria. Thorbjarnarson *et al.*[79] stated that 22 patients had no fasting free HCl, while 10 of these had free HCl values ranging from 8 to 80 units after histamine. Jordan *et al.*[37] believe that tests for gastric acidity give much the same values that are obtained when carcinoma is present. Of the 4 patients in this study with gastric analysis, 2 had a hypochlorhydria and 2 achlorhydria.

The cytologic study of cells obtained from the stomach by lavage or the use of the balloon technique is reported to demonstrate the presence of malignant cells in a large proportion (97 per cent) of neoplasms

of the stomach.[16] Cooper and Papanicolaou,[16] reporting cytologic studies in 4 patients with lymphosarcoma of the stomach, made the diagnosis in 2 instances, considered the third as suspicious of lymphosarcoma and missed the fourth. Rubin and Massey[67] reported the diagnosis of 4 malignant lymphomas out of 50 patients with gastric neoplasms which were studied by this method. Three of these cases were lymphosarcoma of the reticulum cell type while the fourth was diagnosed as Hodgkin's disease. Of interest is that they were able to diagnose a lymphosarcoma involving the second and third portions of the duodenum. Allen *et al.*[2] reported that the cytologic studies performed on 5 patients were all negative. It is very likely that if the growth of lymphosarcoma is predominantly infiltrating and without ulceration, characteristic cells cannot be obtained by the lavage or balloon technique. This procedure was not attempted on any of the cases in the present study.

ROENTGENOLOGIC EXAMINATION

Much has been written regarding the roentgenographic appearance of this process and most of the authors agree that the roentgen findings are not sufficiently characteristic to permit a specific diagnosis of lymphosarcoma of the stomach.[3,7,36,52] Yarnis and Colp[85] felt that gastric lymphosarcoma occurs grossly in two forms: (1) the cells diffusely infiltrate, causing hypertrophy of the rugae and (2) definite tumor formations develop, often with ulceration which may be indistinguishable from carcinoma. Moreton[52] described the following possible roentgenographic findings: (1) The stomach may appear normal; (2) a gastric ulceration may be present; (3) polypoid lesions simulating carcinoma may be the predominant manifestation; (4) an obstructive lesion may be seen.

Feldman,[25] Taylor[77] and Lazarus[42] listed the following roentgenographic findings as being suggestive of lymphosarcoma of the stomach: (1) A filling defect with smooth margins; (2) a localized type of tumor which is round and smooth; (3) involvement of large portions of stomach simulating linitis plastica; (4) mucosal rugae in thick folds; (5) the presence of multiple ulcers. To these findings, Rafsky and associates[61] added: (1) Sluggish or irregular peristalsis and (2) changes in size of the stomach. Weber, Kirklin and Pugh[82] reported that often peristalsis was not so greatly interrupted as in carcinoma. Deeb and Stilson[20] emphasized the remarkable flexibility of the defect as seen fluoroscopically. Jenkinson *et al.*[36] reported that roentgenographically their cases had extensive rather than localized filling defects and that the margins were irregular rather than round and smooth. They also stated that an infiltrating carcinoma is usually less rigid in its earliest phase than later and that lymphosarcomatous infiltrates often result in rigidity which is indistinguishable from carcinoma.

Cardon and Greenbaum felt that the diagnosis of lymphosarcoma of the stomach was difficult for the following reasons: (1) The disease is rare; (2) it mimics carcinoma or ulcer completely in the majority of cases; (3) the differential features seldom appear; (4) some of these differential features occur also in atypical carcinoma, gastritis, syphilis and other diseases of the stomach; (5) suggestive features may not occur until late in the disease.[20] Moreton[52] states "admitting that a specific roentgenologic diagnosis of lymphosarcoma of the gastrointestinal tract is difficult to make, the fact still remains that roentgenologic examination is indispensable for (1) discovering the presence of the lesion; (2) determining in most instances its neoplastic nature; (3) sharply localizing the lesion; and (4) permanently recording the original involvement for the determination of its progression or regression at subsequent examinations."

These lesions are usually diagnosed as benign ulcers, hypertrophic gastritis or carcinoma.[40] None of Snoddy's[72] 34 cases was diagnosed roentgenographically. Crile and associates[17] reported 1 of their 19 cases diagnosed roentgenographically. Thorbjar-

narson and co-workers[79] reported correct diagnosis in 4 of 29 cases. Lame *et al.*[40] and Bartlett and Adams[5] presented well-illustrated cases demonstrating the marked similarity of the roentgenographic findings in carcinoma, hypertrophic gastritis and lymphoma.

In the present study of 13 patients, the possibility of lymphoma was suggested by the radiologist in 1 case. The diagnosis of malignant lesion of the stomach was made in 7 cases; gastric polyps in 1; subphrenic abscess in 1; carcinoma of the pancreas with invasion of the stomach in 1; benign ulcer in 1; hypertrophic gastritis with possibility of lymphoma in 1; and no preliminary examination was made in 1 patient.

GASTROSCOPIC EXAMINATION

Gastroscopy may prove of definite aid in establishing the diagnosis.[18] Schindler in 1922 is reported to be the first to view gastroscopically a stomach containing lymphosarcomatous infiltrates but failed to recognize it as such.[54] Schindler[69] later wrote that the presence of "generalized stiffness of the mucosa with superimposed polyp-like nodules should suggest diffuse lymphoblastoma." Benedict[6] also expressed the opinion that the gastroscopic appearance is definite with the presence of unusually thick rugae, very marked cobblestone mucosa, multiple erosions and ulcerations of various parts of the stomach with or without rigidity or a tumor. Bloomquist[69] was reported to believe that the nodules have a peculiar transparent appearance.

Other authors[11,61,85] felt that the gastroscopic appearance of lymphosarcoma is characteristic enough that the diagnosis may be established. However, Renshaw and Spencer[64] state "at one time one of us thought the gastroscopic appearance of lymphosarcoma was distinctive, but with further experience we do not believe the diagnosis can be made with any degree of certainty." Palmer[54] similarly reported great variation in the gastroscopic appearance of lymphosarcoma.

Renshaw and Spencer[64] reported gastroscopic examination in 8 patients, 6 of whom were diagnosed as having malignant lesions and 2 as having lymphosarcoma. Yarnis and Colp[85] reported correct diagnosis in 2 of 5 patients so examined. Cummins *et al.*[19] described a case with negative roentgen studies in which the gastroscopic appearance suggested a possible lymphosarcoma. A gastric resection was performed and microscopic examination revealed lymphosarcoma.

Thorbjarnarson *et al.*[79] reported that of 9 patients examined gastroscopically, 7 were diagnosed as having carcinoma, 1 as having benign ulcer, and in 1 the lesion was not demonstrated.

One patient in the present study was gastroscoped, the examination revealing large hypertrophic folds in the fundus. No ulcerations or erosions were noted. A biopsy specimen from the posterior wall of lesser curvature was taken through the gastroscope. The microscopic diagnosis was lymphocytic lymphosarcoma. Gastroscopic examination following roentgen therapy demonstrated disappearance of the large folds and replacement by edematous mucosa with a cobblestone appearance. Repeat biopsy disclosed no evidence of malignancy (Case IV).

GROSS PATHOLOGY

Lymphosarcoma has its origin in the aggregates of lymphoid tissue which appear in the submucosa.[24] As the process grows, it invades the mucosa, the muscularis and may extend through the serosa.[52] Involvement of regional lymph nodes occurs frequently (80 per cent).[83]

The gross appearance of lymphosarcoma is not sufficiently characteristic to distinguish it from carcinoma.[17,72] Grossly, these lesions may appear as ulcerations, polypoid formations or diffuse infiltrations.[52] Varying combinations of these gross manifestations may be found in any single case.[7,72,83]

The ulcerative type is reported by Snoddy[72] to be the most frequent. Varying from 1.5 to several centimeters in diameter, it may penetrate only part way through the

muscularis or extend through the serosa, resulting in perforation. The surrounding mucosa may be fairly normal in appearance, thus resembling a chronic benign ulcer. In others the mucosa may be heaped up and indurated, or giant rugal folds may appear. Ulceration of the mucosa is thought to be due to necrosis from pressure and loss of blood supply rather than from malignant invasion proper.[52]

Intrinsic polypoid formations protrude into the lumen of the stomach if the predominant direction of growth is towards the mucosa. These polypoid growths may be single or multiple with poorly defined borders or may appear as well demarcated, bulky lesions.[26]

The infiltrating or intramural type extends along the submucosa and into the muscularis, producing marked diffuse thickening of the stomach wall and giant rugae which grossly cannot be differentiated from hypertrophic gastritis.[40] The extension of the growth in the submucosa results in involvement of the submucosal plexus of nerve endings, thus explaining why pain is frequently unchanged either with a full[52] or an empty stomach.[45]

Foot[26] and Pontius and Witkowski[57] believe that lymphosarcoma can be suspected because of its rubbery feel and its greater resiliency as contrasted to carcinoma.

There may be multiple areas of involvement in any one segment of the gastrointestinal tract, or there may be areas of involvement in several segments of the gastrointestinal tract. Twenty-five per cent of cases are reported to have multiple sites of origin.[2,83]

The stomach may become involved in the generalized form of lymphosarcoma, or secondarily involved from a known focus of lymphosarcoma in some distant part of the body.[9] Buschke and Cantril[9] reported a case with a lesion arising in the region of the right tonsil which developed gastric symptoms fourteen months later. The presence of a gastric lesion was demonstrated roentgenographically and gastroscopically. The lesion completely disappeared after radiation therapy. Jordan *et al.*[37] on reviewing the literature from 1939 to 1954, found 17 cases in which the stomach was involved as a secondary site.

In our files, a gastric lesion developed in one patient with a known lymphosarcoma arising outside the abdominal cavity. This patient had a primary tumor of the nasopharynx, which was treated by irradiation. Six months later he developed gastric symptoms. Roentgenographic studies demonstrated the presence of a lesion in the stomach. This lesion was also treated by irradiation resulting in considerable regression roentgenographically. The patient's symptoms improved and he gained weight but soon generalized extension developed, followed by a gradual downhill course, and he expired ten months after the gastric metastasis. This case has been excluded from the present study because of this origin in the nasopharynx.

HISTOLOGY

There still remains much confusion about the terminology of malignant lesions arising from lymphoid tissue. The malignant lymphomas are commonly divided into lymphosarcoma, Hodgkin's disease and leukemia. The benign forms of lymphoma must be differentiated from the malignant types. Gall and Mallory[30] in 1942 devised the following histologic classification.

1. Stem cell lymphoma } —Reticulum cell sarcoma
2. Clasmatocytic lymphoma } —Reticulum cell sarcoma
3. Lymphoblastic lymphoma } —Lymphosarcoma
4. Lymphocytic lymphoma } —Lymphosarcoma
5. Hodgkin's lymphoma
6. Hodgkin's sarcoma
7. Follicular lymphoma

The first two groups are commonly referred to as reticulum cell sarcoma since they appear to arise from the reticulum cells of the germ centers of follicles and pulp cords.[24] The lymphoblastic and lymphocytic types are grouped together as lymphosarcoma. The lesions classified as Hodgkin's disease are not considered in this study. There is much speculation in the literature that lymphosarcoma may be caused by some infectious or irritating agent but the true etiology still remains unknown.[24]

It is of interest that 4 of the 13 patients in the present study were treated for some other neoplastic lesion. One male had received radiation therapy for epithelioma about the face, one female had been treated for adenocarcinoma of the endometrium, and 2 females had surgery for adenocarcinoma of the breast.

TREATMENT

The treatment of choice is radical surgical removal in those lesions which prove to be resectable.[2,72] If meticulous examination of the surgical specimen grossly and microscopically indicates that the margin of resection is adequate and that no metastases have occurred in the regional lymph nodes, no additional therapy may be necessary. However, if the lesion is incompletely removed or if regional lymph nodes are involved, postoperative radiation therapy is advisable.

In the unresectable lesions, a biopsy should be obtained from the primary tumor to establish the histologic characteristic of the tumor. The removal of an enlarged lymph node from the mesentery or omentum may contain only lymphoid hyperplasia and will fail to prove the histologic nature of the primary lesion. If indicated, a sidetracking procedure should be done and postoperative radiation therapy given to the volume of involved tissue.

Jordan *et al.*,[37] reviewing the literature from 1939 to 1954, collected information on 389 primary lymphomas of the stomach and found an operability rate of 95.7 per cent with an operative mortality of 12.6 per cent. An over-all resectability rate of 75.3 per cent was reported from their review.

Snoddy[72] reported that of the five year or longer survivors collected from the literature (up to 1952), 13 were treated with irradiation only, 21 with surgery only, and 12 with surgery and irradiation. In his own series of 34 cases the 4 surviving five years or longer were treated with surgery only. Since Snoddy's publication, 55 additional patients were reported to have survived five years or longer after treatment; 24 of these were treated by surgery only, 24 by surgery and postoperative radiation therapy, 6 by radiation therapy after biopsy and one received nitrogen mustard after biopsy (Table 1).

Seven of the patients in the present study had surgical resection followed by radiation therapy, 5 patients had radiation therapy following biopsy only, and 1 patient was an operative fatality. Of the 13 patients, 1 lived longer than five years and is well (Case 56, Table 1).

PROGNOSIS

The major factor determining the survival of these patients is whether they actually have a primary lymphosarcoma arising in the stomach or the stomach is involved in an unrecognized generalized lymphosarcomatosis. The differentiation is frequently impossible even at autopsy.[72]

Spontaneous remission and survival in spite of known inadequate therapy by surgery or irradiation are puzzling. Such cases were reported by Taylor,[77] Archer and Cooper[3] and Pund and Stelling.[58]

Madding and Walters,[45] and Jenkinson *et al.*[36] reported that the reticulum cell sarcomas are more resistant to irradiation than the lymphocytic lymphosarcomas. Usher and Dixon in a series of 50 cases including 25 cases of each cell type found no difference in the radiosensitivity of the two.[72] Warren and Lulenski[81] do not believe there is demonstrable difference in radiosensitivity in these two cell types.

Foot[26] feels that there is a close correlation between the microscopic type and life expectancy, reticulum cell sarcoma and lymphoblastoma showing a poorer prognosis than the lymphocytic type lymphosarcoma. McSwain and Beal,[50] however, are of the opinion that survival is influenced more by the site and extent of the growth than by the type of the tumor. Sugarbaker and Craver[76] believe that the inherent quality of the process rather than the histology determines the course of the disease.

A review of the literature by Snoddy,[72] including his own case material, revealed that of the long term survivors 14 had lesions of the small cell type and 5 of the reticulum cell type. Of the long term survivors reported since Snoddy's[72] review, 34 had lymphosarcoma and 16 reticulum cell sarcoma (Table 1).

In the present study, 4 lesions were classified histologically as reticulum cell sarcoma, the other 9 as lymphosarcoma.

The compilation of a five year survival rate in this disease is almost impossible because the published reports include cases which were diagnosed less than five years before publication.

In 474 cases of lymphosarcoma of the stomach collected by Snoddy,[72] 50 five year survivals were noted. Snoddy concluded that the five year survival rate was 10.5 per cent. Jordan *et al.*[37] in their group of 389 primary cases of lymphoma of stomach collected from the literature from 1939 to 1954, found 70 five year survivals with a calculated survival rate of 27 per cent. Both of these values are probably low since many patients who have died were diagnosed less than five years before the articles were published. Allen *et al.*[2] reported a five year survival rate of 58 per cent in patients with resectable lesions. Thorbjarnarson *et al.*[79] noted a 43 per cent five year survival rate in their patients treated by surgery and postoperative irradiation. Burnett and Herbert[8] obtained a 66.6 per cent five year survival rate in patients receiving postoperative irradiation even after inadequate removal of the primary lesion at the time of operation.

The involvement of lymph nodes or of contiguous structures and/or incomplete removal does not preclude the chance of long term survival.[2,35,72,79] In Allen and coworkers'[2] cases, 4 of 12 living more than five years had inadequate removal of the tumor at time of surgery or had lymph node involvement.

Pund and Stelling[58] reported a case of a thirty-seven year old male with biopsy proved lymphosarcoma of the stomach in which only an anterior gastrojejunostomy was performed. The patient was living and well six years later. Stout[75] reported a biopsy proved case which has survived ten years without treatment. In the present case material only 3 of the 13 cases were diagnosed five years or more prior to this writing. One of these is living and well six years and nine months after subtotal gastrectomy and postoperative radiation therapy. Of the other 10 patients, 7 are living and well from twelve months to four years and four months after treatment (Table II).

REPORT OF CASES

The case material used in this study was collected from several hospitals. A brief outline of the history, physical and roentgenographic findings, the histology, type of treatment and results is listed in Table II. A more detailed report on some of the more interesting cases follows:

Case 1. E.S., a fifty-six year old Negro female, was first seen on October 25, 1951 with a history of hematemesis and tarry stools of two to three weeks' duration. On physical examination no peripheral lymph adenopathy was present; no masses were palpable in the abdomen. Laboratory studies: hemoglobin 7.5 gm. Gastric analysis 19 per cent free HCl. Fluoroscopic and roentgenographic examination of the upper gastrointestinal tract on October 27, 1951 revealed an irregular ulceration 3 cm. in diameter just below the angle on the lesser curvature of the stomach. There were some polypoid masses around the area of ulceration and no peristalsis was transmitted through this area (Fig. 1). The impression was that of a malignant lesion of the stomach. On October 31, 1951 a subtotal gastric resection was performed. The histologic report was that of lymphosarcoma with lymph node involvement. From November 15, 1951 to December 10, 1951 the patient received postoperative radiation therapy directed through anterior and posterior opposing fields measuring 10×10 cm. with each area receiving 1,500 r in air. The patient was alive and well six years and nine months after treatment.

Comment. This case illustrates a point emphasized by Allen *et al.*[2] and Snoddy[72] that the occurrence of advanced lesions and

TABLE I

LYMPHOSARCOMA OF THE STOMACH: REPORTED SURVIVALS OF FIVE OR MORE YEARS (SINCE 1952)

Author	Case	Sex	Age	Duration of Symptoms	Cell Type	Gross Findings	Treatment	Follow-Up
Allen *et al.*[2]	1	M	43		Clasmatocytic	Completely removed, negative lymph nodes	Surgery and radiation	22 yr., living
	2	M	49		Clasmatocytic	Completely removed, negative lymph nodes	Surgery only	15 yr., died coronary thrombosis
	3	F	51		Lymphoblastic	Completely removed, negative lymph nodes	Surgery only	15 yr., living
	4	M	52		Lymphoblastic	Liver edge resected, negative lymph nodes	Surgery only	14 yr., living
	5	M	37		Lymphocytic	Resection margin, inadequate	Surgery and radiation	12 yr., living
	6	M	50		Clasmatocytic	Completely removed, negative lymph nodes	Surgery and radiation	11 yr., living
	7	F	55		Stem cell	Completely removed, negative lymph nodes	Surgery and radiation	9 yr., living
	8	F	63		Lymphoblastic	Total gastrectomy and segment of transverse colon, lymph nodes involved	Surgery and radiation	9 yr., living
	9	F	63		Lymphoblastic	Completely removed, negative lymph nodes	Surgery and radiation	8 yr., living
	10	M	38		Lymphocytic	Resection margin, inadequate	Surgery and radiation	7 yr., living
	11	M	62		Clasmatocytic	Resection included tail of pancreas, lymph nodes involved	Surgery and radiation	5½ yr., living
	12	F	68		Clasmatocytic	Completely removed, negative lymph nodes	Surgery only	5½ yr., living
Deeb and Stilson[20]	13	F	37	Gastric distress 7 yr. Duodenal spasms reported 7 yr. earlier	Small cell	Explored with biopsy, lymph nodes involved	Biopsy and radiation	9 yr., living
	14	M	30	Epigastric distress 18 mo. Hematemesis 3 wk. previously	Small cell	Grossly normal, biopsy taken	Biopsy and radiation	7 yr., living
Jenkinson *et al.*[36]	15	M	55	History of duodenal ulcer 24 yr. Recurring episodes of melena, pain in mid-epigastrium 2½ yr.	Lymphocytic	Attached to pancreas 10 cm. in diameter, lymph nodes involved; gastroenterostomy	Biopsy and radiation	12½ yr., living
Wellman and Haines[82]	16	F	54	1½ mo.	Lymphosarcoma	Palpable abdominal mass, lymph nodes involved	Biopsy and radiation	10½ yr., living
Crile *et al.*[17]	17–20						Subtotal gastric resection and radiation	4 living, 5–12 yr.
	21						Subtotal gastric resection	1 dead, 10 yr. postoperatively
Sperling[74]	22	M	52		Lymphosarcoma		Two-thirds gastric resection and radiation	7½ yr., living
	23	F	41		Lymphosarcoma		Two-thirds gastric resection and radiation	6 yr., living
Fruhling and Moutier[29]	24	F	43	4 mo.			Gastric resection and radiation	6 yr., living
Eker and Efskind[22]	25, 26				2-Lymphosarcoma	1 with positive lymph nodes	Partial gastric resection	5 yr. or longer, living
Eker and Efskind[22]	27–29				3-Reticulum cell sarcoma		Partial gastric resection	5 yr. or longer, living
Allen *et al.*[2]	30			2 yr. plus	Lymphoblastic		Biopsy and radiation	6½ yr., died of amyloidosis
Berger *et al.*[7]	31	M	58	Abdominal pain, nausea and vomiting 2 yr.	Lymphocytic lymphoma	Mass involving proximal ⅓ stomach, invading spleen, pancreas and transverse colon	Biopsy and radiation	6 yr. 9 mo., living
Warren and Littlefield[80]	32				Lymphoma, unclassified		Subtotal gastrectomy	5 yr., living
	33				Lymphoma, unclassified		Subtotal gastrectomy	9 yr., living
	34				Lymphoma		Totalgastrectomy	6 yr., living
	35				Lymphosarcoma		Totalgastrectomy	9 yr., living
Thorbjarnarson *et al.*[79]	36	F	62		Lymphosarcoma	Fundus	Esophagogastrostomy	14 yr., living
	37	F	46		Lymphosarcoma	Entire stomach, lymph nodes involved	Total gastrectomy and radiation	Committed suicide 7½ yr. later
	38	M	56		Lymphosarcoma	Lower third	Subtotal resection and radiation	Died suddenly of unknown cause 10½ yr. later
	39	M	29		Lymphosarcoma	Lower third	Subtotal resection and radiation	9 yr., living

TABLE I (*continued*)

Author	Case	Sex	Age	Duration of Symptoms	Cell Type	Gross Findings	Treatment	Follow-Up
	40	F	33		Reticulum cell sarcoma	Pylorus	Subtotal resection and partial resection of liver	11 yr., living
	41	M	46		Reticulum cell sarcoma	Greater curvature	Subtotal resection	15 yr., living
	42	F	59		Reticulum cell sarcoma	Upper two thirds, lymph nodes involved	Total resection and radiation	5½ yr., living
Thomson and Haase[73]	43	F	45		Reticulum cell sarcoma		Biopsy and nitrogen mustard	8 yr., living
Huang *et al.*[35]	44	M	28		Large cell lymphosarcoma		Subtotal resection and radiation	11 yr., living
Hienert[34]	45				Lymphosarcoma	Regional lymph nodes involved	Subtotal resection	5 yr., living
	46, 47				Lymphosarcoma	Regional lymph nodes involved in both	Subtotal resection	6 yr., living
	48				Lymphosarcoma	Regional lymph nodes involved	Subtotal resection	8 yr., living
Burnett and Herbert[8]	49	M	47		Reticulum cell sarcoma		Surgery only	14 yr., living
	50	F	62		Lymphocytic		Surgery only	12 yr. 10 mo., living
	51	F	34		Reticulum cell sarcoma		Surgery only	11 yr. 4 mo., dead
	52	M	58		Lymphocytic	Gross residual disease in liver, pancreas, duodenum and local lymph nodes	Surgery and radiation	10 yr. 7 mo., dead
	53	M	30		Lymphocytic	Gross residual disease in local lymph nodes	Surgery and radiation	7 yr. 5 mo., living
	54	F	41		Lymphocytic	Gross residual disease in omentum, retroperitoneal and local lymph nodes	Surgery and radiation	7 yr. 7 mo., dead
	55	F	59		Reticulum cell sarcoma	Residual disease in gastrocolic region	Surgery and radiation	5 yr. 3 mo., living
Redd	56	F	56	Hematemesis, melena 2–3 wk.	Lymphosarcoma	Multiple ulcers, lesser curvature	Subtotal resection and radiation	6 yr. 9 mo., living

regional lymph node involvement does not preclude a five year cure. The combination of subtotal gastric resection and radiation therapy gives the optimum results in the treatment of advanced lymphosarcoma of the stomach.

CASE II (Courtesy of Drs. J. Sherman, P. Holmes and S. Brown). H.H., a forty year old male, was first seen on March 11, 1954 because of an unexplained left pleural effusion. The chief complaints were shortness of breath, pain in the left lower chest and weakness of three weeks' duration. The patient had had unexplained episodes of diarrhea during the past seven years. These episodes would last from three to four months with 8 to 10 liquid stools daily. No other specific symptoms related to the gastrointestinal tract were noted. The physical examination showed temperature 99.8°F., pulse 110, respiration 24. A questionable mass was present in the left upper quadrant. The laboratory findings were: red blood cell count 4,700,000, white blood cell count 9,400, and hemoglobin 13.2 gm. Three stool examinations were negative for ova and parasites. The bronchoscopic examination demonstrated no abnormal findings. Roentgenologic examination on March 17, 1954 in the anteroposterior view of the abdomen demonstrated a large area in which were numerous small radiolucencies overlying the region of the stomach (Fig. 2). Barium enema study revealed no abnormalities in the colon. A posteroanterior roentgenogram of the chest disclosed fluid in the left lung base. An upper gastrointestinal series was made on March 19, 1954. Fluoroscopy showed the diaphragm to be limited in motion. The stomach was greatly distended and contained considerable amount of material, probably food (Fig. 3). A three hour follow-up roentgenogram demonstrated some retention of barium mixed with food. A possible subphrenic abscess was suspected. On March 24, 1954 an exploratory laparotomy was performed revealing extensive neoplasm involving the stomach with dense adhesions to the omentum, spleen and diaphragm. The enlarged stomach measured some 30 cm. at its greatest length. The stomach wall was very thick, up to 2 cm., with a rough granular serosa. The entire gastric colic omentum was the site of a hard nodular extension. A few nodules were palpable in the lower abdomen on

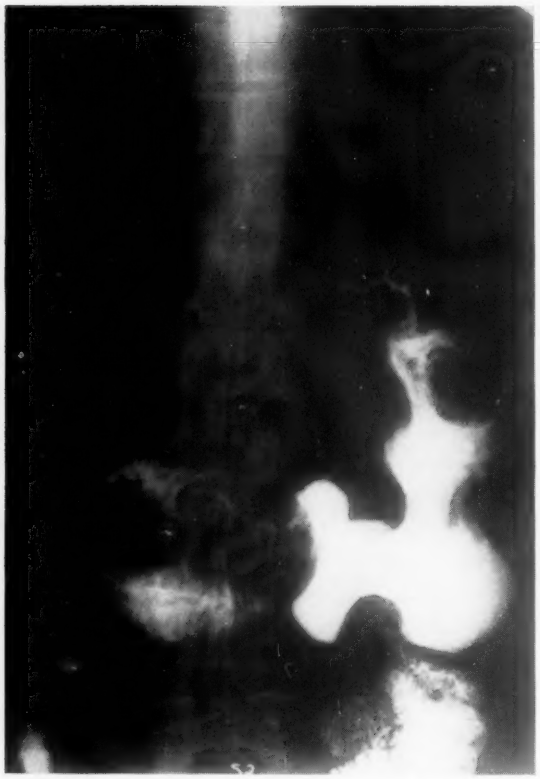

Fig. 1. Case I. A 3 cm. ulcer just distal to angle on lesser curvature with surrounding polypoid mass. Impression: Malignant lesion of stomach.

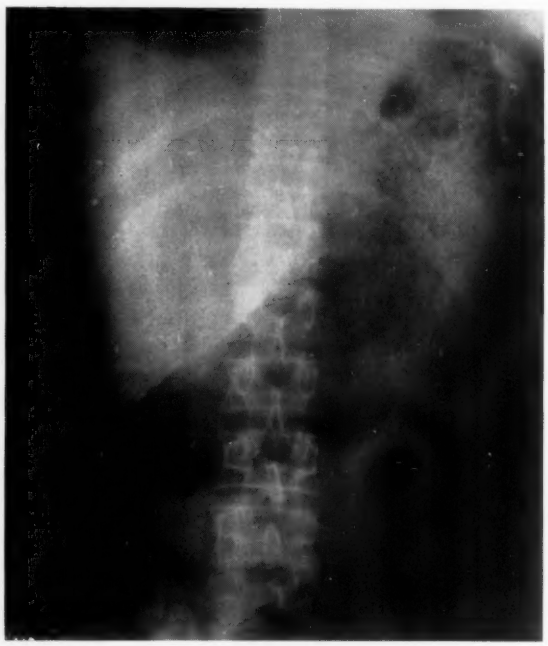

Fig. 2. Case II. Roentgenogram demonstrates marked distention of stomach with retained food material.

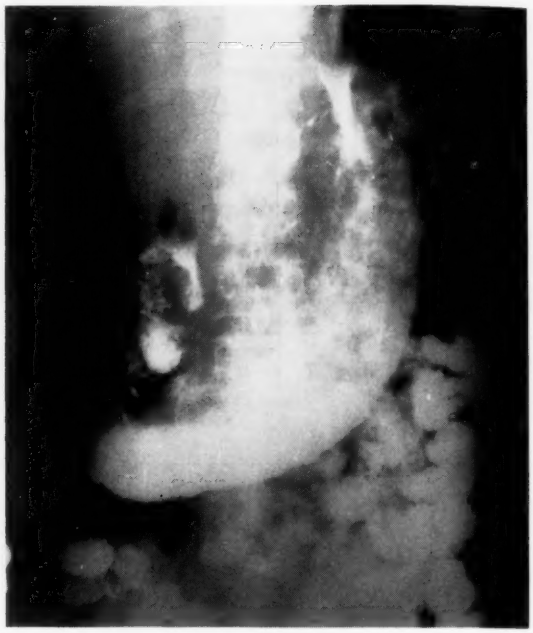

Fig. 3. Case II. Roentgenogram shows enlarged stomach outlined by contrast material.

the serosa of the small bowel. A large lymph node was removed for microscopic study. The histologic report was that of small cell lymphosarcoma. From April through May, 1954 the patient received radiation therapy to the abdomen through anterior and posterior oblique fields measuring 15×20 cm. centered over the upper abdomen. A calculated tumor dose of 2,500 r was delivered. Repeat roentgenograms of the upper gastrointestinal tract revealed reduction in size of the stomach and return of the gastric mucosal pattern to normal. The patient was clinically well four years and four months after completion of treatment.

Comment. This case proves that lesions which may appear nonresectable should be explored when the patient's general condition permits such a procedure. Biopsy for histologic confirmation should preferably be taken from the primary tumor rather than relying on the findings of an enlarged lymph node. The occurrence of diarrhea over a prolonged period of time in this case may have been only coincidental. However, this symptom is reported to have occurred in one of Wellman and Haines' patients.[83] Diarrhea has been reported in extensive

TABLE II

LYMPHOSARCOMA OF STOMACH: AUTHOR'S SERIES

Age	Sex	Symptoms	Abdominal Mass	Roentgenographic Diagnosis	Histologic Report	Treatment	Months after Treatment	
							Dead	Living
27*	M	Pain 14 wk., nausea and vomiting, melena	Yes	Malignant lesion	Lymphosarcoma	Biopsy and radiation	1	
40†	M	Ulcer type pain 11 mo.	Yes	Malignant lesion of stomach	Lymphosarcoma	Subtotal resection and radiation		12
40†	M	Diarrhea, shortness of breath	? mass	Subphrenic abscess	Small cell lymphosarcoma	Biopsy and radiation		52
49	F	Pain 2–3 mo.	No	Benign ulcer	Reticulum cell sarcoma	Subtotal resection and radiation		21
58	M	Heaviness in chest 1 mo., fatigability	No	Malignant ulcer	Reticulum cell sarcoma	Explored	Postoperative death	
56	F	Hematemesis, melena 2–3 wk.	No	Malignant lesion	Lymphosarcoma	Subtotal resection and radiation		81
62	M	Ulcer type pain 2 wk., acute generalized pain	No	No examination	Reticulum cell sarcoma	Subtotal resection and radiation		27
64†	F	Melena, pain 4 mo.	Yes	Cancer of stomach	Lymphosarcoma	Subtotal resection and radiation	30	
65	F	Melena	No	Gastric polyps	Lymphosarcoma	Biopsy and radiation		29
68	F	Pain left upper quadrant 1wk., tenderness and epigastric fullness 1 yr.	No	Hypertrophic gastritis, possible lymphoma	Lymphosarcoma	Biopsy and radiation		34
68	F	Pain upper abdomen 2 mo.	Yes	Cancer of stomach	Lymphosarcoma	Biopsy and radiation	6	
70	F	Postprandial pain 6 mo.	No	Cancer of stomach	Reticulum cell sarcoma	Subtotal resection and radiation	5	
38	M	Ulcer type pains 3 mo.	No	Cancer of pancreas with invasion of stomach	Lymphosarcoma	Subtotal resection and radiation		22

* Courtesy of Dr. Roberts.
† Courtesy of Drs. Sherman, Holmes and Brown.

small intestinal involvement by the lymphoma.

CASE III. H.E.C., a sixty-two year old male, was admitted to the surgical ward on April 26, 1956 with acute generalized abdominal pain and marked rigidity of the abdomen and symptoms of shock. Exploratory laparotomy revealed a 1×1 cm. perforation in the anterior surface of the stomach. A subtotal gastric resection was performed demonstrating a superficial 8×3 cm. ulceration on the greater curvature. The histologic examination showed reticulum cell sarcoma with no lymph node involvement. From July 31, 1956 to August 20, 1956, the patient received radiation therapy to the upper abdomen through anterior and posterior opposing fields measuring 12×15 cm. A calculated tumor dose of 2,665 r was delivered to the midplane of the upper abdomen. The patient had gained weight and showed no evidence of disease twenty-seven months after completion of treatment.

Comment. The presenting symptoms in this patient were those of perforation and acute peritonitis. The involvement of all layers of the stomach wall may result in spontaneous perforation.[2,17,72] In view of this possibility, adequate tissue for histologic examination should be taken from around the site of all spontaneous perforations in the gastrointestinal tract to exclude the presence of a lymphoma.

CASE IV. E.D., a sixty-eight year old female, had noted tenderness in left costal margin, dyspepsia and epigastric fullness for a period of one year. She developed acute pain in the left upper quadrant one week prior to her first visit. Physical findings were noncontributory. On October 13, 1955 an upper gastrointestinal series revealed increased mucosal folds measuring 1 cm. across (Fig. 4). A review of former studies showed that enlarged mucosal folds were already present sixteen months previously. The impression was that of hypertrophic gastritis with a possibility of lymphoma. On October 15, 1955 gastroscopic examination revealed large hypertrophied folds in the fundus, with no ulceration or erosions. At biopsy which was

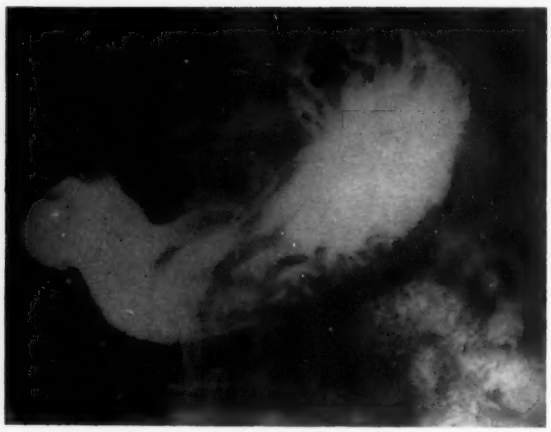

Fig. 4. Case iv. Roentgenogram shows enlarged gastric folds which have been present for a period of sixteen months. Diagnosis: Hypertrophic gastritis, possible lymphoma.

taken from the posterior wall near the lesser curvature, the impression was that of hypertrophic gastritis. Histologic examination showed lymphocytic lymphoma. From October 19, 1955 to November 8, 1955, the patient received radiation therapy to the upper abdomen through anterior and posterior opposing fields measuring 17×17 cm. with 1,500 r in air being delivered to each field. On December 6, 1955 a repeat gastrointestinal series demonstrated disappearance of the hypertrophic gastric folds and the presence of a cobblestone-like mucosal pattern. The stomach was pliable and active peristalsis was noted throughout its entire extent (Fig. 5). On December 7, 1955 gastroscopic examination was repeated. The hypertrophic gastric folds had been replaced by edematous mucosa with a cobblestone appearance. A biopsy was taken. The gastroscopic findings at this time were more suggestive of lymphosarcoma than at the previous examination. Histologically, the gastric mucosa showed acute and chronic inflammation. There was no evidence of malignancy. The patient was alive and well thirty-four months after treatment.

Fig. 5. Case iv. After radiation therapy the enlarged folds are replaced with a cobblestone-type mucosal pattern.

Comment. This case shows the importance of gastroscopic examination in the diagnosis of gastric neoplasms. The use of the gastroscope for visualization of the lesion and obtaining biopsy specimens from involved areas is of value to confirm the diagnosis. Gastroscopy or gastric lavage may also be used to obtain exfoliated cells for microscopic study in patients who could not tolerate an exploratory surgical procedure.

Discussion

The relative increased incidence of lymphosarcoma reported by recent authors[40,53,83] is probably more apparent than real. It may be due to the more frequent use and greater accuracy of diagnostic procedures, and to the exploration of gastric neoplasms with more frequent histologic identification of the tumor types. Lymphosarcoma of the stomach occurs in any age group but, in general, is observed in younger individuals. There appears to be a slightly increased incidence in males, paralleling the distribution seen in carcinoma. The symptomatology is not sufficiently characteristic to permit differentiation from other gastric neoplasms. The duration of symptoms is variable with an average duration of from seven[72] to twenty-six[17] months. Many authors[17,36,37,57] have called attention to the good general physical conditions of these individuals. Mild epigastric tenderness alone or a palpable mass in the upper abdomen may be the only positive finding. Various laboratory procedures may reveal only a slight to moderate anemia with evidence of gastrointestinal bleeding. The gastric analysis may range from an achlorhydria to normal values. The cytologic study of cells obtained by lavage or the balloon techniques may prove to be the

most accurate diagnostic procedure short of performing a biopsy of the primary lesion. The roentgenologic examination confirms the presence of a lesion and its extent but can seldom differentiate lymphosarcoma of the stomach from benign ulcerations, carcinoma or hypertrophic gastritis. Gastroscopy confirms the presence and location of the lesion but offers little evidence to differentiate lymphosarcoma of the stomach from other gastric lesions. Biopsy through the gastroscope or gastric lavage may give histologic proof of the type of lesion. Grossly these lesions can seldom be differentiated from carcinoma; however, their soft, resilient sponge rubber-like consistency is believed to be characteristic by some authors.[26,57] Histologically, many cell types have been identified.[30] There may be difficulty differentiating some of the reticulum cell sarcomas from very anaplastic carcinomas. This can generally be done by employing mucicarmine and reticulum stains.[26]

Radical surgical removal is the treatment of choice in the resectable cases. In those lesions incompletely removed or with evidence of lymph node metastasis, radiation therapy is of definite palliative value and in some cases may effect complete control of the lesion. This latter point has been demonstrated in Case II of our series and in case reports by Burnett and Herbert.[8]

The prognosis in lymphosarcoma of the stomach is much better than in carcinoma of the stomach. Snoddy's[72] over-all five year survival of 10.5 per cent in 474 cases is considered low by some authors. An accurate five year survival rate cannot be compiled from the literature. Allen *et al.*[2] reported a 58 per cent five year survival rate in their resectable cases. By adding to Snoddy's cases the 360 cases published in the literature since 1952 and the 13 cases of our series the total number of reported cases of lymphosarcoma of the stomach at the present is 847. Of the 360 cases since Snoddy's compilation, 55 are known to have survived five years or longer (Table I). Of the 13 cases in the present study 8 are living from nine months to six years and nine months after treatment (Table II).

SUMMARY

1. The reported increased incidence of lymphosarcoma of the stomach is possibly due to the more frequent use of diagnostic procedures.

2. Lymphosarcoma of the stomach occurs somewhat more frequently in males than in females and in a younger age group than does carcinoma of the stomach.

3. The history, physical and roentgenographic and gastroscopic findings are not specific for lymphosarcoma of the stomach.

4. Cytologic studies of cells obtained by gastric lavage or biopsy through the gastroscope may establish histologic proof of a gastric neoplasm.

5. The gross appearance of the lesion is not characteristic; however, its consistency is reported to be more resilient than that of carcinoma.

6. Surgical removal is the treatment of choice. If removal is incomplete or lymph node metastases are present, postoperative radiation therapy is indicated.

7. Every effort should be made to establish the histologic nature of a gastric neoplasm in view of the beneficial effect which may result from radiation therapy in lymphomas.

8. In 1952, Snoddy published an analysis of 474 cases of lymphosarcoma of the stomach, with a 10.5 per cent survival rate. A review of the literature reveals 360 additional cases reported since that time, with 55 five year survivals.

9. Thirteen new cases are added in the present report, one of the them surviving over 5 years.

10. The determining factor in an individual case is whether the lesion arises as a primary focus in the stomach or the stomach is involved secondarily by a generalized process.

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COMBINED RADIATION AND NITROGEN MUSTARD THERAPY IN HODGKIN'S DISEASE AS COMPARED WITH RADIATION THERAPY ALONE*

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THE therapeutic management of Hodgkin's disease has been the subject of many clinical investigations. Roentgen therapy was first introduced in the treatment of Hodgkin's disease by Pusey,[8] Williams,[11] and Senn[9] in 1902 and 1903. As pointed out by Gilbert,[2] however, rational statistics were not available prior to 1920 despite an increasing use of roentgen therapy in the management of this disease. Gilbert[2] attributes this to the use of unperfected apparatus, inadequate methods of dosage measurements, and uncertain diagnosis during that period. Since then numerous excellent studies evaluating the therapeutic management of this condition have been published. With the introduction of the nitrogen mustards as an outgrowth of experience gained in World War II, another means of attacking Hodgkin's disease became available. Numerous chemotherapeutic agents have been investigated but only a few of thousands have proved to be of use clinically.

Regarding Hodgkin's disease as a neoplasm, the aim of therapy in all but the very earliest cases must be to effect the greatest palliative relief, but, at the same time, to produce a prolonged survival in those cases which prove to be exceptionally responsive to treatment. Since 1946 nitrogen mustard has been used at Harper Hospital in most instances, as an adjunctive method of treatment to roentgen therapy. Prior to the introduction of nitrogen mustard, and in patients with definite early involvement of a single lymph node group, roentgen therapy has been used primarily with appropriate general supportive measures. It is believed that no substantial series of cases to date has been reported in which roentgen therapy and nitrogen mustard have been employed concomitantly. Usually nitrogen mustard has been used in an alternating fashion after radioresistance has developed. It is the purpose of this study to assess the results of a therapeutic plan in which nitrogen mustard and roentgen therapy are administered simultaneously in cases showing evidence of generalized disease from the outset.

CLINICAL MATERIAL

Three hundred and ninety-two patients with histologically verified Hodgkin's disease observed at Harper Hospital during the period 1922–1957 constitute the material for this study. All cases which have had treatment are included and all survival dates are taken as from the time of original diagnosis and treatment until the time of death, or until the time the patient was lost to follow-up studies. No case has been excluded because of loss to follow-up; these are presumed dead. In this manner the series of cases can be more directly compared with other published studies. Because of the inherent difficulty in true staging of Hodgkin's disease, no attempt has been made to separate these patients into groups as to localized or generalized involvement.

ABSOLUTE SURVIVAL RATES

Three hundred and forty-seven patients were treated between 1922 and 1952 and thus are suitable for long term analysis. Table 1 gives the absolute survival rates

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TABLE I

ABSOLUTE SURVIVAL PERCENTAGES

	Total No. of Cases	No. of Survivals	Per Cent
	30 Years		
Males	21	2	9.5
Females	14	1	7.1
	35	3	8.6
	25 Years		
Males	48	4	8.3
Females	21	1	4.7
	69	5	7.1
	20 Years		
Males	79	8	10.1
Females	37	4	10.8
	116	12	10.2
	15 Years		
Males	120	14	11.6
Females	64	10	15.6
	184	24	13
	10 Years		
Males	176	33	18.7
Females	99	18	18.2
	275	51	18.5
	5 Years		
Males	216	77	35.6
Females	131	43	32.8
	347	120	34.6

from five years up to thirty years in this group. The absolute five year survival for the entire group amounted to 34.6 per cent. These absolute five year survival figures are compared with numerous previously published series, particularly those of Nice and Stenstrom[5] (25 per cent), Slaughter and Craver[10] (17.7 per cent), Medinger and Craver[4] (24 per cent), Elkins[1] (25 per cent), Paterson and Paterson[6] (25 per cent) and Peters and Middlemiss[7] (38 per cent).

Table II gives the absolute five year survival rates according to age distribution in

TABLE II

FIVE YEAR SURVIVALS, AGE DISTRIBUTION IN DECADES (1922–1952)

Decades	Total No. of Cases	No. of Five Year Survivals	Per Cent
0–10			
Males	12	5	41.6
Females	2		
Total	14	5	35.7
11–20			
Males	33	16	48.4
Females	16	5	31.2
Total	49	21	42.8
21–30			
Males	54	22	40.7
Females	28	14	50
Total	82	36	43.9
31–40			
Males	49	18	36.7
Females	33	14	42.4
Total	82	32	39
41–50			
Males	27	8	29.6
Females	25	8	32
Total	52	16	30.7
51–60			
Males	31	5	16.1
Females	14	1	7.1
Total	45	6	13.3
61–70			
Males	8	1	12.5
Females	9	1	11.1
Total	17	2	11.7
71–80			
Males	2	2	100
Females	4		
Total	6	2	33.3
Total	347	120	34.6

decades at the time of referral. It may be noted that, although the male patients outnumber the females by almost 2 to 1, there is little real difference in the survival rates. Table III gives the five year survival rates from date of initial treatment, divided chronologically into 5 periods. This table illustrates that a definite improvement in the results was obtained in the fourth and fifth periods.

Table III

FIVE YEAR SURVIVALS FROM DATE OF INITIAL TREATMENT (1922–1952)

	Total No. of Cases	No. of Five Year Survivals	Per Cent
	1922–1928		
Males	20	5	25.0
Females	14	4	28.5
	34	9	26.4
	1929–1934		
Males	32	12	37.5
Females	9	3	33.3
	41	15	36.1
	1935–1940		
Males	43	10	23.5
Females	17	5	29.4
	60	15	25
	1941–1946		
Males	52	22	42.3
Females	43	14	31.8
	95	36	37.9
	1947–1952		
Males	69	28	40.6
Females	48	17	35.4
	117	45	38.4

COMPARATIVE ANALYSIS IN A SPECIAL GROUP

In addition to presenting the over-all survival figures of a large group of cases of Hodgkin's disease, it is our purpose to carefully analyze the effects of the combined use of nitrogen mustard and roentgen therapy in both, long term results and the production of palliation and remissions. To aid in this analysis the group of patients treated in the fourth and fifth periods, from 1941 to 1952, is given special attention. During the fourth period roentgen therapy alone was used, except in 12 cases in which subsequently recurrence developed and later combined roentgen therapy and nitrogen mustard were employed. During the fifth period 31 cases were treated by roentgen therapy alone and 85 cases by combined roentgen therapy and nitrogen mustard. In the latter cases the addition of nitrogen mustard was the only significant variable factor. In studying the five year results for the fourth and fifth periods (Table III), it may be noted that aside from a slight improvement in the over-all results of those treated in the fifth period, there appears to be little significant difference. However, if the cases treated with roentgen therapy alone and those treated by the combined method are considered separately (Table IV), we find a 37.2 per cent survival in those patients treated with roentgen therapy alone and a 39.2 per cent survival in those treated by the combined method. We believe that this percentage is particularly important because of the fact that, although no formal division into stages is made in this presentation, those patients in whom nitrogen mustard was used were those in whom more than one lymph node group was involved, or in whom there was other evidence of generalized disease. Combined therapy was most often employed at the time of original referral but in those cases in which recurrence and generalization developed later, the combined method was almost universally applied.

In a further attempt to exactly assess the contribution of nitrogen mustard, the same group of patients was divided into subgroups showing the three year survival rates and a comparison was made of those

TABLE IV

FIVE YEAR SURVIVALS, ROENTGEN THERAPY ALONE VERSUS ROENTGEN THERAPY COMBINED WITH NITROGEN MUSTARD (1941–1952)

	Total No. of Cases	No. of Five Year Survivals	Per Cent
Roentgen Therapy Alone			
Males	65	29	44.6
Females	45	12	26.6
Total	110	41	37.2
Roentgen Therapy Combined with Nitrogen Mustard			
Males	56	21	37.5
Females	46	19	41.3
Total	102	40	39.2

treated by roentgen therapy alone and those in whom a combination technique was used (Table v). By this procedure we found a definite trend suggesting that there is an advantage in the combined method, the percentage of three year survivals being 45.3 per cent in the subgroup treated by roentgen therapy alone and 49.4 per cent in the subgroup treated by the combined method. This increase in the palliative results is supported by the fact that the average monthly survival of the patients expiring during the first five years following referral was 5.6 months longer in those cases which had benefit of both roentgen therapy and nitrogen mustard (Table vi).

TABLE V

THREE YEAR SURVIVALS FROM DATE OF INITIAL TREATMENT (1941–1952)

Date of Initial Treatment	Total No. of Cases	No. of Three Year Survivals	Per Cent
Roentgen Therapy Alone			
1941–1943	53	26	49
1944–1946	35	14	40
1947–1949	20	9	45
1950–1952	11	5	45.4
Total	119	54	45.3
Roentgen Therapy Combined with Nitrogen Mustard			
1941–1943			
1944–1946	8	6	75
1947–1949	46	24	52.2
1950–1952	39	16	43.6
Total	93	46	49.4

Peters and Middlemiss[7] have shown a high first year mortality of 34 per cent in their series of 291 cases. In our series the first year mortality is also proportionately high, 27.8 per cent for the 392 cases. It was found, however, that in the twelve year period from 1941 to 1952 only 17.5 per cent failed to survive the first year where this combined method was used (Table vii). Again, this figure is more significant when we realize that only those patients with more than local involvement had combined roentgen therapy and nitrogen mustard at the time of referral.

RESULTS IN RECURRENCES

Of further interest is a group of 32 cases in which combined roentgen therapy and nitrogen mustard were used when reactivation or generalization of the disease occurred after previous roentgen therapy. None of these patients had nitrogen mustard until at least one year after the original treatment, the average interval being 48.4 months (Table viii). The average prolongation of life in this group amounted to forty-four months, or three years and eight months, with 6 patients still living. The average total survival of these patients to date, including the 6 living patients, has been 92.6 months, or seven years and six months. (The deficit of the 27.8 per cent over-all first year mortality contributes to this long average survival rate, but we believe this group also illustrates the advantage of combined therapy in chronic Hodgkin's disease.) As compared to the entire group, the 6 living patients have to date an average survival of 174.2 months, or fourteen years, six months since the time of the original referral. It is also to be noted that their combined treatment was not in-

TABLE VI

AVERAGE MONTHLY SURVIVAL OF PATIENTS EXPIRING IN THE FIRST FIVE YEARS

	Total No. of Cases	Roentgen Therapy Alone		Roentgen Therapy with Nitrogen Mustard	
		Expired in First Five Years			
		No.	Average Mo. Survival	No.	Average Mo. Survival
1922–1940					
Males	95	68	19.4		
Females	40	28	19.6		
Total	135	96	19.5		
1941–1952					
Males	121	38	16.8	33	24.2
Females	91	32	18.4	28	21.8
Total	212	70	17.5	61	23.1

stituted until an average of 87.1 months after the completion of the former roentgen therapy series. This fact is additional proof of the more favorable prognosis in those patients with chronic slowly recurring disease.

TECHNIQUE OF ROENTGEN THERAPY

The roentgen therapy employed in the earlier years of the series under study consisted of 200 kv. peak, 1 mm. Cu filtration, half value layer of 1 mm. Cu. Later 225–250 kv. constant potential, 2 mm. Cu or Thoraeus filtration and a half value layer of 2.5–3 mm. Cu were used. In addition, patients with mediastinal involvement were treated with roentgen rays generated at 500 kv., 7 mm. Cu filtration and a half value layer of 9 mm. Cu. This higher energy permitted a higher percentage depth

TABLE VII

PERCENTAGE OF PATIENTS EXPIRING IN THE FIRST YEAR

	Total No. of Cases	Roentgen Therapy Alone			Roentgen Therapy with Nitrogen Mustard		
		No. Treated	Expired First Year		No. Treated	Expired First Year	
			No.	Per Cent		No.	Per Cent
1922–1940							
Males	95	95	27	28.4			
Females	40	40	12	30.			
Total	135	135	39	28.8			
1941–1952							
Males	121	65	21	32.3	56	9	16.1
Females	91	45	14	31.1	46	9	19.5
Total	212	110	35	31.8	102	18	17.5

TABLE VIII

OVER-ALL SURVIVAL OF PATIENTS TREATED WITH ROENTGEN THERAPY ALONE ONE YEAR OR MORE BEFORE COMBINED THERAPY

	Total No. of Cases	Average Survival		Total Average Survival	
		Roentgen Therapy Alone (mo.)	Combined Therapy (mo.)	(mo.)	(yr.)
Males	19	58.2	46.4	104	$8\frac{3}{4}$
Females	13	34.5	40.4	74.9	$6\frac{1}{4}$
Total	32	48.4	44	92.6	$7\frac{1}{2}$
Males	14	52.5	34.5	87	$7\frac{1}{4}$
Females	12	33.3	32.4	65.7	$5\frac{1}{2}$
Expired	26	43.6	33.7	77.3	$6\frac{1}{4}$
Living	6	87.1	87.1	174.2	$14\frac{1}{2}$

dose in the chest and minimized pulmonary fibrosis. Treatment was administered over involved peripheral lymph node areas, such as the cervical, supraclavicular, infraclavicular, axillary, inguinal, femoral and, less commonly, the epitrochlear, suboccipital and popliteal areas. Where evidence of generalization of the disease was present such as fever, pruritus, or palpable abdominal masses, treatment was also directed to the upper abdomen and pelvis. This latter group generally had nitrogen mustard, after its availability, in addition to roentgen therapy.

TECHNIQUE OF NITROGEN MUSTARD THERAPY

Nitrogen mustard (methyl bis (β-chloroethyl) amine hydrochloride) was given in the amount of 0.1 mg. per kg. of body weight daily for four consecutive days. Roentgen therapy was administered in the morning and a saline infusion was started in the afternoon. The mustard preparation was then injected into the intravenous tubing. The incidence of thrombophlebitis is very low in our experience, when proper care is exercised. As recently stated by Karnofsky,[3] the incidence of nausea and vomiting is a frequent complication. This can be effectively minimized with appropriate medication. Depression of white blood cells occurs as well as thrombocytopenia, but this seldom proves to be troublesome since the availability of antibiotics has more or less paralleled the introduction of nitrogen mustards. Tri-ethylene melamine has been employed in a limited number of patients but is of no obvious superiority.

SUPPORTIVE THERAPY

The administration of whole blood is important where indicated, but this is not often necessary except in advanced stages of the disease. Antibiotics, iron, vitamins and other chemotherapeutic agents have been used generally where proper medications warranted them.

SUMMARY AND CONCLUSIONS

A total of 392 cases of Hodgkin's disease was treated at Harper Hospital from 1922 through 1957. Of these, 347 were suitable for long term follow-up study. The absolute survival rates are presented in five year series from five years to thirty years.

A special group of 212 cases (1941–1952), approximately one-half of which was treated by roentgen therapy alone and the other half by a combination of roentgen therapy and nitrogen mustard, is analyzed in detail. The fact that an almost equal

absolute five year survival rate was observed in each group is interpreted as indicating an advantage of the combined method, since this was used only in cases of generalized involvement. The increased three year survival rates, the longer average monthly survivals of deceased patients and the lower first year mortality rate are additional observations in support of the more beneficial value of the combined method as compared to roentgen therapy alone. In those cases where the combined method was used for the treatment of recurrence, worthwhile further remissions have been produced.

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HEMANGIOPERICYTOMA*

A REPORT OF FOUR CASES WITH A REVIEW OF THE LITERATURE

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SINCE the original article of Stout and Murray[11] in 1942, 57 cases of hemangiopericytoma have been reported in the literature. To these we are adding 4 cases, bringing the total to 61.

In their original article Stout and Murray described 9 patients with this disease; to these Stout added 25 in 1949.[13] In this series are included the cases reported by Kaplan[6] and Ackerman and Warren,[1] as well as one of the cases reported by Sims, Kirsch and MacDonald.[10] Reviewing 350 cases of soft tissue tumor from the pathology file of the Cleveland Clinic, McCormack and Gallivan[9] have been able to remove 14 cases which they re-classified as hemangiopericytoma. Nine other isolated case reports have appeared in the literature by various authors: one arising in the extrarectal tissue by Bacon, Sherman and Campbell;[3] one in the sigmoid colon by Ault, Smith and Castro;[2] one in the thigh by Forrester and Houston;[5] one in the leg by Kent;[8] one in the omentum by Stout and Cassel;[12] one in the rectum by Kay and Warthen;[7] one in the meninges by Begg and Garrett;[4] and 2 by Wise,[14] one arising in the axilla and one in the abdomen.

INCIDENCE

The relatively few cases recorded in the literature do not reflect the true incidence of the disease since many cases are not reported. In a personal communication to Warthen[7] in 1951, Stout stated that he had seen 110 examples of the tumor. Tabulation of all the reported cases, including the 4 we are presenting, shows that the disease occurs in both sexes and at all ages, from the neonatal period through senescence, with a predilection for the middle decades as shown in Figure 1. It has been seen in 3 newborn infants by Stout and Murray.[11] The oldest reported patient was ninety-two years of age.[12] There were in all 31 males and 29 females; the sex of one patient is not reported.

PATHOLOGY

The chief cellular component of hemangiopericytoma is the pericyte, originally described by Zimmerman as a modified smooth muscle cell closely applied to the capillary wall and serving as a regulator of the size of the capillary lumen. Stout and Murray[11] in 1942 demonstrated by means of tissue culture that this same pericyte gives rise to the epithelioid cell of the glomus tumor. The separation of hemangiopericytoma from the glomus tumor and other related groups was first suggested by Stout and Murray because the tumor lacked the cellular organization of the glomus tumor and because of the neuromyoarterial component. The absence of pain and its ability to infiltrate tissue, as well as its aggressiveness as demonstrated by local recurrence and distant metastasis, also make hemangiopericytoma distinctly different from the glomus tumor, which is encapsulated and nonmalignant.

Hemangiopericytoma can be differentiated from capillary hemangiomata in that the cellular proliferation in the latter is derived from the endothelial cells within the lumen, while in hemangiopericytoma the tumor cell is derived from the pericyte outside the vascular wall. This can be easily demonstrated by means of a silver reticulum stain which blackens the capillary sheath and separates the cells within the

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lumen of the vessel from those without (Fig. 2).

Stout postulated two prerequisites for the diagnosis of this tumor: (1) The endothelial cells must retain their normal appearance and be separated from the pericytes by a fibrous sheath and (2) the proliferating tumor cell must be the pericyte.

CLINICAL FEATURES

Hemangiopericytoma has as wide a distribution throughout the body as the capillaries and pericytes. The 34 cases reported by Stout and Murray have occurred in the following locations: 6 in the upper extremities; 6 in the lower extremities; 6 in the head and neck; 5 in the trunk; 5 in the retroperitoneum, mesentery and omentum; and one each in the orbit, tongue, pericardium, diaphragm, ileum and meninges.

The presenting symptom is usually a mass varying in size from a 1 cm. nodule to 10–20 cm. in diameter. The tumor is usually firm, circumscribed and, at times, nodular. Although clinically and at surgery the tumor often appears encapsulated, this is seldom confirmed microscopically. The capsule is frequently infiltrated with tumor cells. The skin over the mass shows no discoloration or redness to suggest its vascular nature. This is explainable by the fact that the blood vessels are obliterated and the lumen is a potential space compressed by the proliferating pericyte.

Pain when present is due to the enlarging soft tissue mass compressing the neighboring nerves.

The rate of growth of the tumor varies greatly. The hemangiopericytoma of the omentum reported by Stout and Cassel[12] was known to have been present for at least sixty years. Several cases of hemangiopericytoma where the known duration of the tumor was over fifteen years have been reported. In many others, however, the disease has been rapidly fatal. Stout has stated that there are no criteria available that would permit one to predict whether or not the tumor is malignant. Of the 110 cases that came to his attention up to 1951, Stout found that 21 per cent showed recurrence and 12.7 per cent showed distant metastasis.

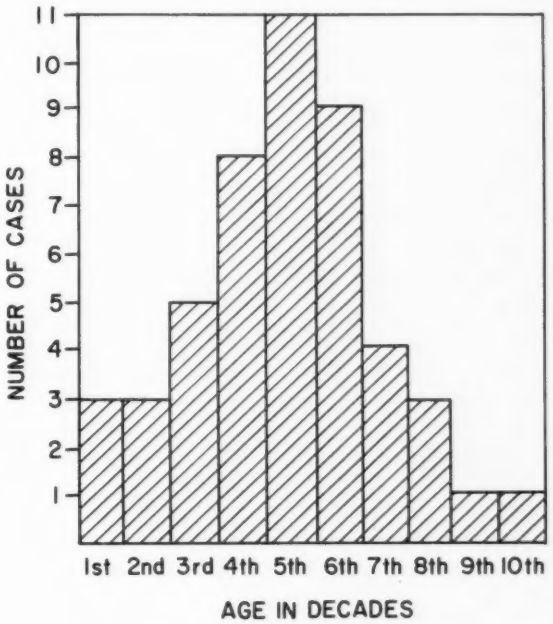

Fig. 1. Age Distribution.

ROENTGEN APPEARANCE

The roentgenographic finding is usually that of a soft tissue mass which may be well demarcated. Pressure erosion on the adjoining bones is sometimes seen as described and illustrated by Kent.[8] Calcification in the tumor mass may be present and was seen in 3 cases by Stout and Cassel[12] and in the single cases described by Ackerman and Warren,[1] and by Kent,[8] as well as in one of our own (Case IV). No roentgenographic description of the calcification is given except in Kent's case, which was stated to be in the form of spicules of calcium deposit in the tumor mass. In our case the calcification had a whorl-like appearance and suggested a vascular tumor. Hemangiopericytoma cannot be differentiated from other soft tissue sarcomas by its roentgenographic appearance alone. The presence of calcification often suggests angiosarcoma. Metastasis, if present, in-

TABLE I

MANAGEMENT OF THE PRIMARY LESION AND RESULTS IN 61 CASES OF REPORTED HEMANGIOPERICYTOMA

No. of Cases	Management	Results
10	Treatment not mentioned	
41	Removed surgically	13 had local recurrences 1 had 10 recurrences 1 had 3 recurrences 1 had 2 recurrences 10 had 1 recurrence 28 either not followed up or had no recurrence 10 had metastasis following initial removal
10	Radiation therapy following biopsy or incomplete surgical removal	9 patients showed improvement

dicates its malignant nature. Metastatic lesions to the chest and bone from hemangiopericytoma cannot be distinguished from other sarcomatous metastases.

TREATMENT

Most authors reporting on hemangiopericytoma have limited their discussions to the clinical and pathologic aspect of the disease or to the reporting of single cases. A discussion of the treatment of this tumor is difficult because of the insufficient data available. As more cases are reported, it is expected that the treatment will be evaluated more fully and a clearer opinion of the management will be formed.

In 10 of the 61 cases reported there is no mention of the treatment given. Forty-one cases have been treated with surgical excision alone. Ten had surgical excision and postoperative radiation therapy or radiation therapy alone with variable results as shown in Table 1.

As may be seen, surgical excision was the only form of treatment in the majority of the reported cases. It is interesting to note that of these 41 patients, several had had one or more recurrences at the site of the lesion requiring re-excision. One patient had 10 local recurrences in eleven years,[11] one had three,[13] one had two,[13] and 10 had had one recurrence at the time they were reported.

The remaining 28 patients were either not followed-up or showed no recurrence. The tendency of the tumor to recur locally following excision as noted by several authors is, therefore, well substantiated. Distant metastasis is also frequent and has been reported in 10 patients in this group. None of these patients received prophylactic radiation therapy to the operative site. They all had a surgically removable tumor. Nevertheless, the incidence of local recurrence and distant metastasis is high. One wonders what the effect of prophylactic postoperative radiation therapy would be. It is conceivable that it could cause a decrease in the incidence of recurrence and metastasis and possibly find its best use in this group. Since the behavior of any particular hemangiopericytoma is unpredictable from the microscopic picture as mentioned above and in view of the high rate of local recurrence, it would seem desirable to irradiate the operative site of all resected lesions.

Of the 10 patients who received radiation therapy, in 2 no attempt was made to remove the tumor. It was decided to institute radiation therapy after securing a biopsy. Both had adequate doses. One, reported by Stout,[13] showed shrinkage of the tumor, with relief of pain following therapy; the other reported by Kent[8] showed no decrease in the size of the primary tumor which, however, became softer. This patient is interesting in that he also had had bilateral pulmonary metastases. One side only was irradiated in order to study the effect of roentgen therapy on the tumor. The irradiated side became roentgeographically free of metastases and remained so for four months. At autopsy, seven months later, the treated lung was found to be much less involved with metas-

tases than the untreated lung.

Two patients had radiation therapy following removal of the primary mass. One reported by Sims *et al.*[10] had a tumor located in the region of the left scapula which recurred ten months following electrodesiccation. This patient received three doses of 425 r each at monthly intervals to a 4 cm. field with 2 mm. Al filtration. There was complete involution of the lesion. The other patient reported by Stout[13] had a cystic mass measuring 8.5 by 7.8 by 6.7 cm. removed from the region of the lower left ureter. Excision was incomplete and three months later he received 7,200 r in air, given in 24 doses through multiple ports during a two month period. This reduced, but did not completely eliminate, the thickening at the site of the operation.

Four more patients, one reported by Stout,[13] one by Wise,[14] one by Forrester and Houston,[5] and one by McCormack and Gallivan,[9] received radiation therapy either to the primary lesion or for distant metastases. The dose given in these cases is not specified, but all, except Forrester and Houston's case, seemed to have derived some benefit from irradiation either in the form of relief of pain, arrest of growth or decrease in the size of the mass.

Two of the patients we are presenting received roentgen treatment. One (Case II) had a postoperative course consisting of 4,930 r tumor dose through two portals to the right arm. The tumor, nevertheless, recurred a year later. The other patient (Case IV) received 7,100 r tumor dose with 2 mev. to a metastatic mass in the chest. The mass shrank to about half its original size and the patient experienced improvement in dyspnea and relief of pain. Roentgen treatment to a metastatic lesion in the left pubic bone was also beneficial in reducing the pain following the administration of 3,400 r tumor dose with 2 mev.

In summary, 10 patients were treated with radiation therapy, either to the primary lesion when not completely removed or to its metastasis. Nine showed beneficial effects in the form of decrease of the size of the mass, reduction of pain or arrest of growth.

REPORT OF CASES

Case I. 543451. H.N. This twenty-three year old white female was admitted to The New York Hospital on July 11, 1949 with the chief complaint of swelling in the left upper arm of two months' duration. The swelling was painless with no numbness, throbbing or tingling sensation. Physical examination showed a 10×10 cm. soft tissue mass on the outer aspect of the left arm. The mass was slightly tender and not attached to the bone or the skin. Five days after admission a local removal of the tumor was performed. At operation it was felt that the entire tumor was removed and sent to the surgical pathologic laboratory. The specimen was 5×5×2.5 cm. weighing 34 gm. and fairly well encapsulated. Microscopic study revealed the tumor to be highly cellular, composed of fibroblasts some of which were spindle shaped. A silver stain emphasized the numerous capillaries throughout the tumor and the perivascular arrangement of the neoplastic cells. The slide was examined by Dr. A. P. Stout who agreed with the diagnosis of hemangiopericytoma.

It was decided to give the patient roentgen treatment but she did not keep her appointments, and four months after the local excision she had a recurrence at the site of the original lesion. A left humeral disarticulation was performed on November 25, 1949 and the patient was discharged three weeks later. Subsequently, she entered another hospital and expired on March 18, 1950, ten months after the tumor was first noticed. The record of the patient could not be obtained from the other hospital.

Case II. 182952. M.M. This fourteen year old white female was admitted to The New York Hospital on December 15, 1949 complaining of swelling in the right arm of ten months' duration. There was no pain, tenderness or erythema. The past history was significant only in that she had been admitted to The New York Hospital four years earlier for a tumefaction in the left inguinal area, which was excised and reported as tuberculous lymphadenitis.

Physical examination disclosed a 4–5 cm. hard, slightly movable mass on the lateral aspect of the right arm in the region of the

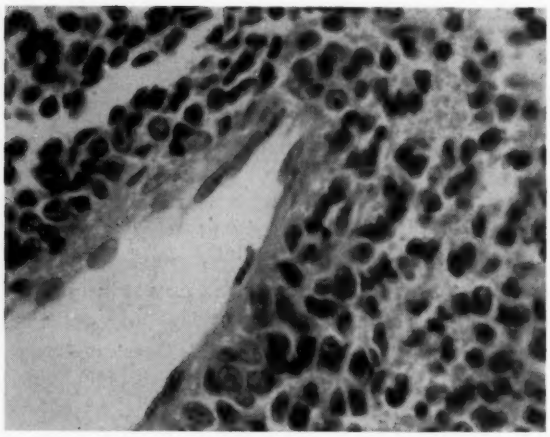

Fig. 2. Case II. Photomicrograph showing a large blood vessel with normal endothelial lining and a collagen sheath surrounded by a large number of proliferating tumor cells with rounded or slightly elongated nuclei and fine chromatin material.

deltoid insertion. The mass was not attached to the skin and caused no impairment of muscle function. Local excision of the mass was done. The specimen consisted of two irregular fleshy masses of tissue, the larger measuring 5×3×2 cm. and the smaller 1.5×1×1 cm. Microscopic examination (Fig. 2) showed cells arranged in a mosaic pattern; their cytoplasm blended imperceptibly into those of adjoining cells; the nuclei were round or oval with many intermediate forms, and in other areas they were spindle shaped and very hyperchromatic. A large number of vascular channels were found coursing through the cellular elements, and there was a readily apparent perivascular predilection of the tumor cells. A diagnosis of hemangiopericytoma was made.

The patient was treated with 250 kv. roentgen rays and received a 4,930 r tumor dose given through two 14×8 cm. portals, one medial and one lateral at 15 ma. and 50 cm. target-skin distance over a period of twenty-four days.

Approximately a year after the initial admission, the patient reentered The New York Hospital for a recurrence of the tumor at the original site. On physical examination the right arm was diffusely enlarged. The mass was excised again on December 8, 1950. The microscopic picture was similar to that obtained from the original lesion. An additional 4,550 r tumor dose was given through two portals. The same physical factors were used.

About sixteen months after the first admission, the patient was readmitted for the third time because of difficulty in breathing. Physical examination showed ptosis of the right eyelid, miosis and enophthalmos. A chest roentgenogram revealed massive pleural effusion and a left hilar mass.

She then entered another hospital for symptomatic treatment and terminal care. She expired on September 10, 1951, less than two years after her original admission to The New York Hospital. An autopsy showed massive pulmonary and pleural metastases.

Case III. 747284. C.S. This white male aged sixty-five was admitted to The New York Hospital on September 8, 1956 because of a lump on the left arm of three months' duration. There were no associated pain, weakness or abnormalities. Physical examination was noncontributory except for a fixed firm mass 4×7 cm. (Fig. 3*A*) on the lateral aspect of the left arm in the region of the deltoid insertion. A roentgenogram of the left arm showed a soft tissue density in the mid arm with no calcification or bone involvement. Laboratory examinations, including complete blood cell count, blood urea nitrogen, alkaline phosphatase, Mazzini test and urinalysis were negative. The electrocardiogram and chest roentgenogram were normal.

A biopsy of the soft tissue mass was reported as hemangiopericytoma. On September 13, 1956 a radical excision of the mass was performed. The tumor was found to be encapsulated and wrapped around the bone but not attached to it. The mass measured about 8 cm. in diameter, and on sectioning, it was found to be smooth pale yellow-tan and somewhat gelatinous in character. Microscopic examination showed the tumor to be composed of sheets of delicate collagenous stroma which formed a syncytium. The slightly hyperchromatic middle sized nuclei were mostly spindle shaped or round. A peculiar relationship between the vasculature and the tumor cells was noted, the latter being densely packed around the blood channels. There were numerous mitotic figures.

Fifteen months after the first admission, the patient re-entered the hospital complaining of a recurrence of the mass in the left arm. On examination, a 5×6 cm. rounded mass was felt in the left arm at the lower end of the scar from the previous operation. A similar mass was also felt at the upper end of the incision. Roentgenograms showed no bone involvement in the

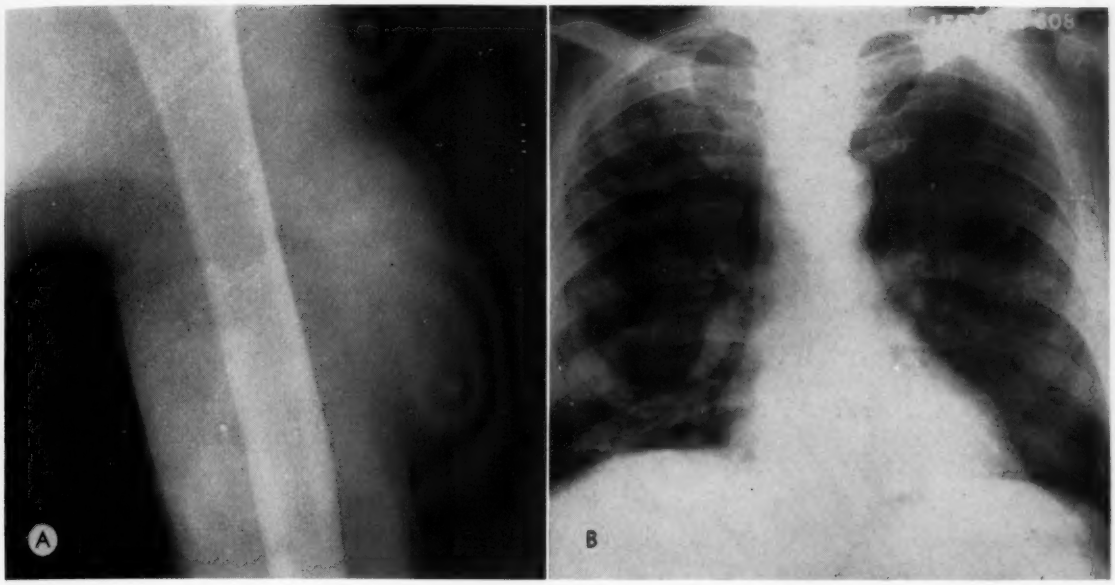

Fig. 3. Case III. (*A*) Roentgenogram showing a 4×7 cm. mass on the lateral aspect of the left arm. No soft tissue calcification or bone erosion. (*B*) Metastases in the right base fifteen months after the initial surgical removal of the primary tumor.

arm; the chest, however, demonstrated evidence of metastases in the lungs (Fig. 3*B*). After a local excision of the tumor, the patient was discharged. The microscopic study was again reported as hemangiopericytoma.

Case IV. This thirty-three year old white female was admitted to the Beekman Downtown Hospital on June 25, 1956 complaining of swelling of the right leg of two years' duration. Her present illness began in February of 1954 when, while three months pregnant, she noticed tenderness of the calf of the right leg. This was thought to represent varicose veins. The tenderness persisted and in July of 1955 a swelling of the right calf led to the suspicion of a tumor. A roentgenogram of the right leg was negative except for a faint calcification in the region of the calf muscles (Fig. 4*A*).

Physical examination on admission to the hospital was unremarkable except for a tumor mass in the region of the right calf following the contour of the gastrocnemius muscle, moderately hard and tender. A roentgenogram of the right leg (Fig. 4*B*) showed an amorphous calcific mass in the calf area. There was no evidence of erosion or infiltration of bone. The calcification was much more extensive than the faint calcific stippling noted on the submitted roentgenograms taken ten months earlier and suggested a whorl-like formation. A chest roentgenogram was reported negative. A local but incomplete excision of the tumor was performed. The mass removed measured 6×4×4.5 cm. It was nodular and covered with a fibrous tissue capsule defective at one pole. The cut surface had a slight tan color. The microscopic examination showed spindle shaped cells resembling fibroblasts surrounding many tortuous cleft-like endothelium-lined spaces devoid of blood cells. The endothelial cells were well differentiated throughout. Moderate mitotic activity with minimal nuclear pleomorphism was exhibited by the tumor cells located outside the vessel walls as shown by a reticulum fiber stain. A Masson trichrome stain revealed no myofibers in association with the tumor cells. A diagnosis of hemangiopericytoma was made.

A supracondylar amputation was advised and carried out three weeks after excision of the tumor. The patient was discharged in a good condition.

Approximately a year later, the patient started to complain of dyspnea and chest pain on deep inspiration. A chest roentgenogram (Fig. 4*C*) showed a mass along the upper left cardiac border with a smooth outline and in close contact with the heart. This was treated with rotational therapy at 2 mev. to a total tumor dose of 7,100 r in fifty-eight days delivered through a 12×12 cm. portal for the

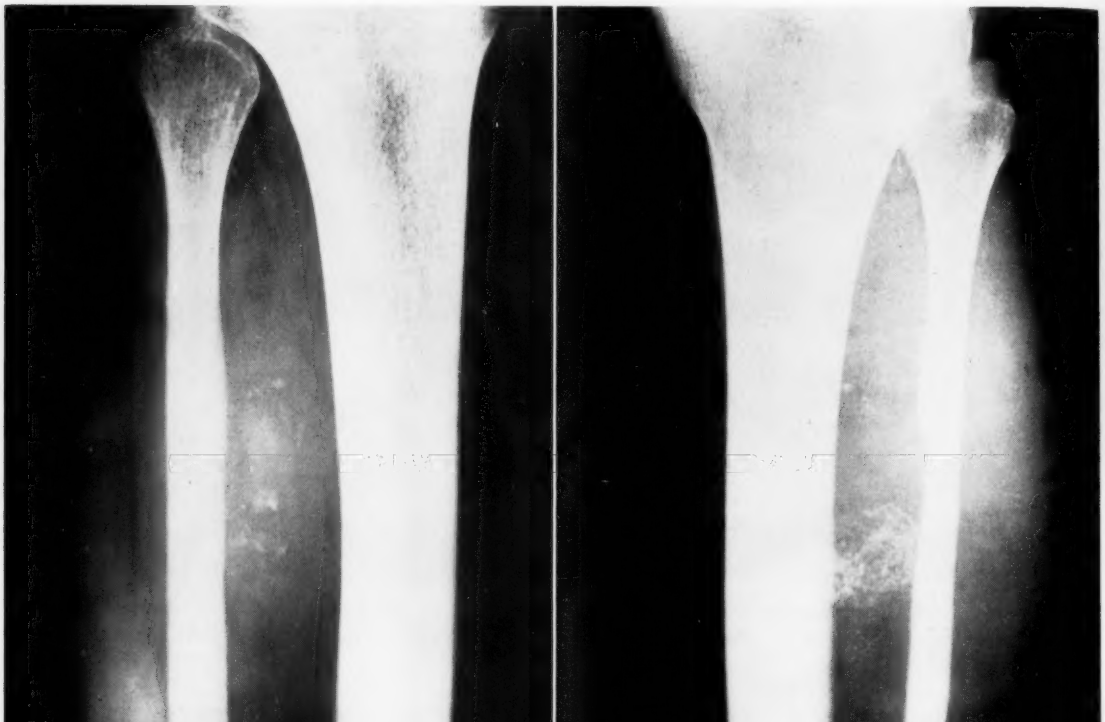

FIG. 4. Case IV. (*A*) Roentgenogram showing the calcific deposit in the soft tissue of the right leg. (*B*) Marked increase in the calcific deposit ten months later which now has a whorl-like appearance.

first 21 treatments and a 10×10 cm. portal for the last 10 treatments. At the end of therapy, the chest pain had disappeared and the tumor mass shrank to half its original size.

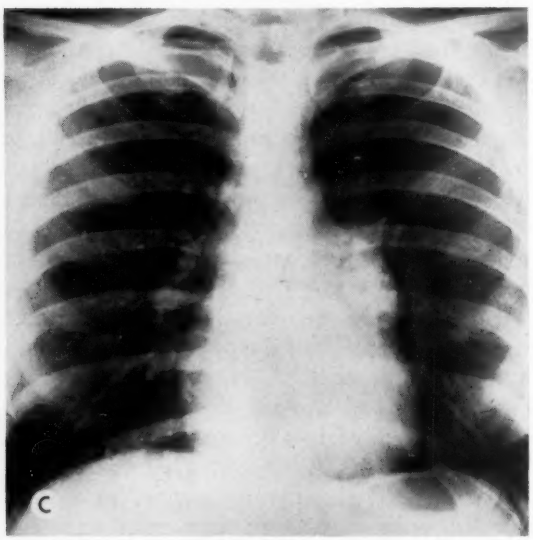

FIG. 4. Case IV. (*C*) Metastasis to the left hilus.

On January 28, 1958 the patient complained of pain in the left femoral area. A skeletal survey demonstrated an osteolytic metastasis in the right parietal area measuring 12 mm. in diameter (Fig. 4*D*) and a lytic lesion in the superior ramus of the left pubis measuring 2 ×7.5 cm. (Fig. 4*E*). The latter received a 3,400 r tumor dose in seventeen days through a 10×10 cm. portal at 2 mev. The pain disappeared following roentgen therapy and when last seen in March of 1959 she had no complaint except for a mucositis at the vaginal introitus.

CONCLUSIONS

Many pathologists have recognized hemangiopericytoma as a definite entity. Their cases, added to the cases reported and seen by Stout and colleagues, form the basis of our knowledge of the disease.

Although sometimes benign, the malignant nature of hemangiopericytoma is evident. Three of our 4 cases showed local recurrence. Two had distant metastases and

Fig. 4. Case IV. (*D* and *E*) Metastasis to the skull and left pubis.

2 died of the disease, one sixteen months and another eight months after the initial admission. One of the 2 that are still alive had a second excision of a recurring mass three months ago, and the other is suffering from widespread metastases to the skull, lung and pelvis. The incidence of local recurrence and metastases in our 4 cases is higher than the 21 per cent recurrence rate and the 12 per cent metastases stated by Stout. All our cases, however, occurred in the extremities, a site reportedly more prone to malignancy and aggressiveness than other locations throughout the body.

Very few reports in the literature discuss the roentgenographic appearance. The available evidence, however, indicates that hemangiopericytoma appears as a localized soft tissue mass which may cause pressure erosion on bones and occasionally shows calcification. The diagnosis of hemangiopericytoma cannot be made by roentgen examination alone, but should be considered in the differential diagnosis of soft tissue tumors.

Most of the reported cases have been treated primarily by surgical excision. Radiation therapy has been given for the treatment of metastases, or for lesions incompletely removed at surgery. Although meager, the available evidence on the use of radiation therapy in primary or metastatic hemangiopericytoma indicates that some benefit could be obtained from this form of treatment when complete surgical excision is not possible. The most important use of radiation therapy, however, is possibly in the early cases when a complete excision of the tumor is attempted. This group shows a high incidence of local recurrence, and radiation therapy with an adequate dose may well eliminate a large number of these recurrences and reduce the incidence of metastasis.

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Vol. 82, No. 4

INCIDENCE OF NEOPLASIA AFTER IRRADIATION OF THYMIC REGION*

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CONCERN with "thymic enlargement" began about fifty years ago[3] and reached its maximum in the mid-thirties. It was believed that an enlarged thymus gland contributed to a number of untoward effects, including compression of the trachea and fetal atelectasis; also, that it played an unknown role in the so-called "thymicolymphatic" constitutional type. Thymic enlargement was sometimes suspected to be of significance in the sudden unexplained deaths of infants and children.

It is well to note that the normal range of the size of the thymus gland is difficult to determine since it is not easily measured. Roentgenographic examination of the chest of infants and children became a common method of attempting to determine the size of the thymus gland. Several factors that influenced the appearance of the mediastinal silhouette on chest roentgenograms, including the stage of respiration and rotation of the patient, were frequently underestimated and, as a result, many cases were diagnosed as "thymic enlargement." Such a diagnosis, made either on the basis of the interpretation of a chest roentgenogram or because of certain clinical manifestations thought to be due to an enlarged thymus, was followed for a number of years almost routinely by irradiation of the thymic region in an attempt to decrease the size of the thymus gland. The dosage and the technical factors used varied considerably from one institution or office to another, but it is now recognized that this irradiation of infants and young children may well have been significant in the increased incidence of certain types of neoplasia among those so treated.[1,2,7]

At the University Hospital, Ann Arbor, Michigan, considerable interest was devoted to the thymicolymphatic constitutional type. The possible association of hypertrophy of the thymus gland and other lymphoid elements with hypoplasia of the aorta and other vascular structures and hypoplasia of the adrenal gland was being postulated. As a result of this general concern, from 1932 to 1954 routine chest roentgenograms were made of most newborn infants born here and of children referred here for any reason.

This routine of obtaining chest roentgenograms for the purpose of demonstrating the thymic region was further simplified by the general acceptance of the terms "thymic study" or "thymus films" when requesting this type of examination. Over the years the interpretation of these roentgenograms gradually changed, so that considerable variation in the size and shape of the mediastinal shadows was considered normal. However, a review of the reports of these roentgenograms from 1932 to 1951 is illuminating. Variations in position and degree of inspiration were minimized and particular attention was given to the "supracardiac shadow" and its degree of widening. The degree of deviation or angulation of the trachea, particularly posteriorly, was the subject of considerable comment. Occasionally, the trachea was described as being narrowed or notched by the increased pretracheal soft tissues. The summary of the reports frequently included the words "enlarged" or "hyperplastic thymus" and in the older children the term "persistent thymus" was used. There were, of course, a gamut of clinical symptoms mentioned on

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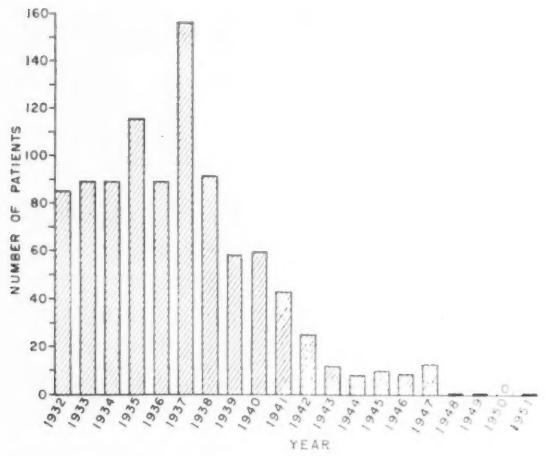

Fig. 1. Number of patients whose thymic region was irradiated from 1932 to 1951 at the University Hospital.

Table I

AGE DISTRIBUTION OF PATIENTS WHOSE THYMIC REGION WAS IRRADIATED

Age Group	No. of Patients	
0– 2 mo.	576	
3– 6 mo.	118	
7–12 mo.	60	
		754
1– 3 yr.	154	
4– 6 yr.	20	
7–12 yr.	1	
More than 12 yr.	8	
Uncertain	21	
		958

the roentgenographic requisitions as being possibly associated with thymic enlargement.

If there was some evidence on the chest roentgenograms of what was thought to be thymic enlargement or if there were clinical symptoms ascribed to thymic enlargement and occasionally described as "thymic symptoms," the infant or child was referred to the Division of Radiation Therapy for consideration of irradiation of the thymic region. Occasionally, a child without roentgenographic evidence of thymic enlargement but who had some difficulty with anesthesia would also be referred for irradiation. It was the custom to wait four days after the completion of the radiation treatment before proceeding with anesthesia and the contemplated surgical operation. Frequently, check-up chest roentgenograms were obtained and many of these were interpreted as showing reduction of the thymic enlargement.

Because of the increased interest in the possible long term effects of the irradiation of the thymic region of infants and children, we felt it worthwhile to review the patients who were so treated at the University Hospital. The radiation therapy records, including the details of the irradiation, as well as the hospital records are readily available for review of all persons treated since early in the year 1932. The task of obtaining information on the current status of the patients and whether or not they have had any serious disease was accomplished by the Follow-up Unit of the University Hospital, which is part of the Tumor Registry.

MATERIAL

From 1932 through 1951, 958 patients received radiation treatment of the thymic region. Figure 1 shows the number of patients treated in each year. The largest number, 157, was treated in 1937 and after 1941 there was a rapid decrease in the number treated. During the past ten years, only 3 patients have been treated in

Table II

DEPARTMENT IN WHICH PATIENTS WHOSE THYMIC REGION WAS IRRADIATED WERE REGISTERED

Obstetrics (newborn)	374	
Oral Surgery	203	
Pediatrics	192	
General Surgery	47	
Otology	42	
Orthopedic Surgery	33	
Radiation Therapy	20	
Neurosurgery	15	
Ophthalmology	13	
Others	19	
		958

Table III

SUMMARY OF DOSAGE USED FOR IRRADIATION OF THYMIC REGION FROM 1932 TO 1951

Dosage (air)	No. of Patients
100 r or less	
×1	34
×2	15
×3	33
101 r–150 r	
×1	40
151 r–200 r	
×1	661
×2	121
×3	40
×4	3
Other	11

Interval between treatments was usually 3 to 7 days.

this manner, the last in 1951. Of the 958 cases, 567 or 59 per cent were male. Table 1 shows the age distribution of the patients treated. Well over half of the total number or 576 cases were treated before two months of age and 754 or 79 per cent were treated before one year of age. There were a few older children and 2 adults (over twenty-one years) who also received radiation therapy.

The service or department in which the patient was registered is shown in Table II. Of the entire group, 374 or 37 per cent were born at the University Hospital. This group is of interest because it is representative of newborn infants anywhere and should have only the expected incidence of congenital abnormalities and other diseases of the general population. The remainder, 584 patients, were referred to the University Hospital. The 20 registered in the Division of Radiation Therapy and perhaps a few in the group registered in the Department of Pediatrics were referred for suspected thymic enlargement, but the rest, over 550, were referred for some unrelated condition and the thymus was evaluated and the thymic region irradiated only as a secondary procedure. The relatively large number, 203, registered in the Department of Oral Surgery reflects the reputation and activity of that department in the repair of congenital abnormalities of the face and mouth. The correlation of suspected thymic enlargement or of subsequent disease with an obvious congenital abnormality present in at least 203 cases is a matter of speculation.

TECHNIQUES OF IRRADIATION

The dosage and technical factors used to treat the thymic region varied considerably over the period of this study. Table III gives a summary of the dosage used, and shows the number of patients who were treated in each general dosage range. A course of treatment consisted of either one, two, or three treatments and if more than one treatment were given, the usual interval of time between treatments was three to seven days. The most commonly used dose, administered to 661 patients, was 200 r, as measured in air, given once. The minimum dose was 30 r administered three times at

Table IV

SUMMARY OF TECHNICAL FACTORS USED FOR IRRADIATION OF THYMIC REGION FROM 1932 TO 1951

Voltage and Distance	Filtration			
	0	4 mm. Al	0.25 mm. Cu+1.0 mm. Al	0.5 mm. Cu+1.0 mm. Al
130–135 kv.				
30 cm. target skin distance	—	132	89	1
150 kv.				
50 cm. target skin distance	37	2	612	7
200 kv.				
50 cm. target skin distance	2	1	8	81

TABLE V

SUMMARY OF VARIATIONS OF TREATMENT TECHNIQUES USED FOR IRRADIATION OF THYMIC REGION FROM 1932 TO 1951

Approximate Period	kv.	Target Skin Distance (cm.)	Filtration	Field Size (cm.)	Dose (r in air)
1932	130	40	4 Al	6× 6	30×3
			0.5 mm. Cu+1 mm. Al		60×3
1932–1933	135	30	0.25 mm. Cu+1 mm. Al	6× 6	200×3
1934–1940	150	50	0.25 mm. Cu+1 mm. Al	10×10	200
1941–1943	200	50	0.5 mm. Cu+1 mm. Al	10×10	200
1944–1948	150	50	0	10×10	125
				6× 6	50
1949–1951	200	50	0.5 mm. Cu+1 mm. Al	6× 6	100

an interval of one week or 50 r administered once. The maximum dose given at any one time to a child was 320 r. The largest total dose used was 1,000 r but this was divided into 3 courses over a period of two years. One child received 800 r in divided doses of 200 r each in a two week period. Ten patients whose thymic region was irradiated are known to have had previous irradiation of this region elsewhere but the details are unknown. In addition, twenty-three of these patients also received radiation treatment at the University Hospital for some other condition, such as hemangioma or hyperplastic lymphoid tissue in the nasopharynx. The variations in the technical factors are shown in Table IV. The most commonly used factors were 150 kv., 50 cm. target skin distance and 0.25 mm. Cu+1.0 mm. Al filter and a half-value layer of about 1.0 mm. Cu. The most commonly used field was an anterior mediastinal field 10×10 cm. in size. Table V shows the variations in treatment techniques in an approximate chronologic order. The largest number of patients was treated from 1934–1940, with the dose and factors mentioned above. It is of interest to note the gradual increase in dosage used from 1932 to 1934 and the definite decrease in dosage used after 1944.

The most frequently used dose and technique, 200 r given once to a 10×10 cm. field employing 150 kv., 50 cm. target skin distance, and 0.25 mm. Cu+1 mm. Al filtration, produced the following depth doses: skin surface, 272 r; 1 cm. depth, 266 r; 2 cm. depth, 244 r; 3 cm. depth, 218 r; 4 cm. depth, 190 r; 5 cm. depth, 166 r; and 10 cm. depth, 82 r. At 3 cm. the calculated energy absorbed was 207 rads.

METHODS OF FOLLOW-UP STUDY

In order to determine the subsequent course of the 958 patients whose thymic region had been irradiated, the Follow-up Unit reviewed the Hospital Records to obtain addresses and other facts that would provide means of contacting the patient or his family. A general form letter was sent to the parents' last known address asking about the patient, his health and whether he had had any serious diseases. No mention was made of the previous irradiation. A second form letter was then used, addressed to the patient. Subsequently, letters and phone calls to relatives, county clerks, police, and state bureaus of vital statistics were used to obtain follow-up information. In view of the fact that many of the patients had not been seen at the University Hospital for twenty to twenty-five years, the accomplishment of the Follow-up Unit was very satisfactory. If the patient or family indicated that any type of tumor, mass, cyst, lump, or cancer had developed, specific details were requested and, if possible, physicians contacted and

TABLE VI

STATUS OF FOLLOW-UP INFORMATION OF 958 PATIENTS WHOSE THYMIC REGION WAS IRRADIATED FROM 1932 TO 1951

(July 1, 1958)

Complete Follow-up Information (1957–1958)	861	
Incomplete Follow-up Information (5/11, 10/5, 12/3, 16/10, 22/0, 24/11)	6	
Follow-up Information Available		867
No Follow-up Information	54	
Patients Put Up for Adoption (Not Followed)	37	
		958

pathology slides reviewed. If death had occurred, the death certificate information was obtained.

RESULTS OF FOLLOW-UP STUDY

The status of the follow-up information as of July 1, 1958 is shown in Table VI. Of the 958 persons who were irradiated, follow-up information was available on 861 patients. We had considered this information complete if we had received word that the patient was alive, well and had no serious illnesses within the last eighteen months. If there was any suggestion that a neoplasm of any nature had developed or had been treated, every attempt was made to obtain complete information. Six patients without complete information available were known to be alive at the intervals shown. The designation 5/11 in Table VI indicates that the follow-up information was available five years and eleven months after the thymic region was irradiated. All efforts to obtain follow-up information failed in 54 cases. In addition, 37 illegitimate newborn infants whose thymic region was irradiated were not followed. Including this group of 37 patients and assuming credit for the incompletely followed group of 6, the over-all percentage of follow-up was 90.5 per cent.

The response to our follow-up efforts was most gratifying. The vast majority of patients and parents were eager to cooperate and pleased that someone was interested in their welfare. Even if a death had occurred, the responding letters or calls were usually appreciative of our interest.

Of the 867 with follow-up information available 99 or 11.4 per cent had died. This figure seems relatively high, but it should be noted that over half of the treated group came to the University Hospital for some other, frequently serious, unrelated condition. Of the 374 infants born at the University Hospital, 37 were illegitimate and 28 have not been followed. Of the remaining 309, 18 or 5.8 per cent had died.

The interval of time of observation and the number of living patients are shown in Table VII. Twenty-seven patients have been followed for over twenty-five years but none for as long as twenty-six years. The number of "patient years" was determined by multiplying the number of full years of observation by the number of patients. The total figure of 15,130 patient years is shown in an attempt to convey the

TABLE VII

INTERVAL OF OBSERVATION OF LIVING PATIENTS. LENGTH OF TIME FROM DATE OF IRRADIATION OF THYMIC REGION TO DATE OF LAST FOLLOW-UP CONTACT

Interval (yr.)	No. of Patients	Patient Years
25–26	27	675
24–25	72	1,728
23–24	67	1,541
22–23	88	1,936
21–22	83	1,743
20–21	97	1,940
19–20	103	1,957
18–19	48	864
17–18	71	1,207
16–17	44	704
15–16	19	285
14–15	8	112
13–14	9	117
12–13	9	108
11–12	13	143
10–11	7	70
Less than 10	3	—
Total	768	15,130

TABLE VIII

INTERVAL OF OBSERVATION OF THE 99 PATIENTS WHO HAVE DIED. LENGTH OF TIME FROM DATE OF IRRADIATION OF THYMIC REGION TO DATE OF DEATH

Interval (yr.)	No. of Patients	Interval (yr.)	No. of Patients
0–½	45	11–12	3
½–1	13	12–13	2
1–2	7	13–14	0
2–3	6	14–15	3
3–4	0	15–16	1
4–5	2	16–17	3
5–6	3	17–18	1
6–7	1	18–19	2
7–8	1	19–20	1
8–9	1	20–21	2
9–10	1	21–22	1
10–11	1		

size or magnitude of the sample observed. The average period of observation for the entire group of 867 was over seventeen and one-half years.

The interval of time of observation of the 99 patients who have died is shown in Table VIII. Nearly one-half of this group died within six months of the time they were irradiated and 58 or 59 per cent died within one year of the time they were irradiated. Again it is important to note that many of those who died had some unrelated condition at the time of the irradiation of the thymic region.* Table IX is a summary of the cause of death of these 99 patients. Almost one-half of them died of the original condition for which they were seen at the University Hospital or of some complication related to this situation. The acute infections as shown on the death certificates included whooping cough, "cholera infantum," tracheobronchitis, and meningitis. The term pneumonia was classified in 2 cases as lobar and in 3 others with some specific location but the rest were vague. All of these deaths occurred within four years after the irradiation of the thymic region. The nature of the accidents was

* For statistical analysis the total patient years of observation included the time of observation up to date of death of each of the patients. This total figure is 15,506 patient years.

TABLE IX

SUMMARY OF CAUSE OF DEATH OF 99 PATIENTS WHO HAD IRRADIATION OF THYMIC REGION

Original condition for which patient was seen at University Hospital	40
Acute infection other than pneumonia	14
Pneumonia	9
Accident	13
Neoplasm	6
Operative death	3
Other	14
	99

varied: 7 of the 13 were automobile accidents, 2 were drowning, the others included asphyxia in a cave-in of a sand tunnel, a fall, a burn and a gun shot wound. The group labeled "others" includes one who was seen at University Hospital at four months of age because of cyanotic attacks and died at six months of age, the death certificate indicating "thymic death." In 2 other patients who died here and were autopsied,

TABLE X

CAUSE OF DEATH OF 18 OF THE 309 PATIENTS BORN AT UNIVERSITY HOSPITAL WHOSE THYMIC REGION WAS IRRADIATED FROM 1932 TO 1951 WITH FOLLOW-UP INFORMATION

Cause of Death	Interval from Irradiation to Death yr./mo.
Tracheo-esophageal fistula	1 da.
Congenital stenosis of ureters	1 da.
Atelectasis neonatorum	9 da.
Tracheo-esophageal fistula	11 da.
Acute bronchitis	0/1
Pulmonary atelectasis	0/1
Whooping cough	0/2
Whooping cough	0/3
Dehydration and acidosis	0/5
Tracheobronchitis	0/6
Fall from window	4/0
Burn	4/6
Lymphatic leukemia*	5/7
Astrocytoma of cerebellum*	8/5
Lymphosarcoma*	10/1
Automobile accident	11/—
Gun shot wound	12/11
"Epileptic seizures"	14/0

* Cases which subsequently developed malignant neoplasm.

comment was made of use on a hyperplastic thymus, hypoplasia of aorta, myocardium and adrenals. One of these patients died seven hours after a craniotomy for evacuation of a subdural hematoma, thought to be due to birth trauma and the other was found to have an internal hydrocephalus and bronchopneumonia. It is of interest to note that 38 of the 99 patients who are dead had some definite congenital abnormality. The cause of death of the 18 patients who were born here is shown in Table x and represents a pattern of the causes of death similar to that observed in the general population without the influence of selectivity of being sent to a referral hospital. The cases shown with the asterisk subsequently developed a malignant neoplasm.

Eleven patients referred to the University Hospital with a neoplasm had their thymic region irradiated. Table xi lists this group of patients and shows the type of neoplasms present at the time of this irradiation and what the subsequent course has been. Three of the group of 11 died because of their neoplasm and one died of intercurrent disease. The only patient still alive who had a malignant neoplasm at the time of the irradiation of the thymic region had a Wilms' tumor and received preoperative radiation treatment followed by nephrectomy. In this group the irradiation of the thymic region was, of course, incidental.

The neoplasms or tumors that developed after the irradiation of the thymic region are shown in Table xii. The order in which the neoplasms are listed is in ascending age of the patient at the time the neoplasm developed. A malignant neoplasm is indicated by an asterisk. The osteochondroma of the right humerus, which developed in patient No. 1, may have arisen in an area included in the field of irradiation. The lesion was known to be present at the age of four. At the age of fifteen it was removed apparently because of some pressure on adjacent structures. Patient No. 3 developed leukemia at the age of five. The death certificate indicates that it was lymphatic leukemia; the microfilmed hospital record

Table XI

NEOPLASM PRESENT WHEN THYMIC REGION WAS IRRADIATED

Neoplasm	Age When Irradiated	Status and Interval Since Irradiation (yr./mo.)
Brain Tumor	4 mo.	dead 0/1
Wilms' Tumor	21 mo.	dead 0/3
"Hemangioma of Central Nervous System"	6 mo.	dead 0/9
Sacral Teratoma	2 mo.	dead 2/10 (pneumonia)
Wilms' Tumor	13 mo.	alive 19/4
Hemangioma, leg	3 wk.	alive 23/4
Neurofibromatosis	6 mo.	alive 23/11
Hygroma colli	6 wk.	alive 24/4
Hemangioma, buttock	2 mo.	no follow-up
Hemangioma, knee	2 wk.	no follow-up
Lymphangioma, buttock	7 da.	no follow-up

of another hospital indicates that it was the acute form in duration and clinical manifestations. Patient No. 4 died here during an attempted resection of a large tumor of the cerebellum. Patient No. 5 died elsewhere at ten years of age of what was listed as lymphosarcoma on the death certificate. Also mentioned were leukopenia and hemorrhages, further indicating that the cause of death was some type of lymphoblastoma. Patient No. 6 was seen at the University Hospital originally for a cleft lip and congenital keratitis. At the age of nine years he was seen elsewhere with an enlarged thyroid gland and what appeared to be lymphogenous type of pulmonary metastases. There was significant uptake of I^{131} over the thyroid and chest. A thyroidectomy was done and multiple cervical metastases removed. The pathology diagnosis was mixed papillary and alveolar carcinoma with true neoplastic follicles producing colloid. The patient received several courses of I^{131} therapy postoperatively. The pulmonary metastases gradually regressed and ultimately disappeared. At present, five and one-half years since

TABLE XII

NEOPLASMS OR TUMORS THAT DEVELOPED AFTER THE THYMIC REGION WAS IRRADIATED

Patient No.	Neoplasm or Tumor	Age When Irradiated	Age When Developed Tumor (yr.)	Status and Interval Since Irradiation (yr./mo.)
1	Osteochondroma, right upper humerus	1 wk.	4	alive 17/3
2	Cystic Hygroma, neck	9 da.	5	alive 16/7
3*	Acute Lymphatic Leukemia	10 da.	5	dead 5/7
4*	Astrocytoma, cerebellum	9 da.	8	dead 8/5
5*	Lymphosarcoma	10 da.	9	dead 10/1
6*	Carcinoma of Thyroid	2 mo.	9	alive 14/11
7	Popliteal Mass	5 mo.	9	alive 13/5
8	Hamartoma-like lesion, neck	2 mo.	12	alive 22/4
9	Bone cyst, os calcis	1 da.	13	alive 24/8
10	"Breast Tumor"	9 wk.	14	alive 25/5
11	Hamartoma-like lesion, mediastinum	6 wk.	14	alive 19/4
12	Cyst, neck	3 yr.	15	alive 24/1
13	Lipoma, left shoulder	3 yr.	16	alive 23/6
14	"Ovarian Tumor"	4 mo.	16	alive 22/3
15	Fibroadenoma, breast	8 wk.	18	alive 22/5
16	Osteochondroma, left ilium	2 yr.	18	alive 19/6
17	"Tumor"	newborn	20	alive 21/2
18*	Chondroma, right anterior chest wall	1 mo.	22	alive 23/7
	Carcinoma, cervix *in situ*		22	
19	"Tumor"	2 mo.		alive 21/10

* Cases that developed malignant neoplasm.

the thyroidectomy, there is no definite evidence of the neoplasm. Patient No. 7 developed a mass in the popliteal space which was subsequently excised. The pathology diagnosis was a nonspecific chronic inflammatory process. Patient No. 8 developed a mass in the lower cervical region at the age of twelve. Six years later, this mass was excised and since, over four years, the patient has been well. Review of the sections of the surgical specimen indicated that this was either the end result of an old hyalinizing lymphadenitis or a hamartoma-like lesion. A similar histologic appearance was observed in a lesion removed from the hilus of patient No. 11. This patient was seen here originally because of a talipes equinovarus deformity. A routine chest roentgenogram in 1951 at the age of fourteen showed a lesion in the left hilar region. A lobectomy was done and, at first, the lesion was considered a thymoma but later the opinion was changed and it was considered a hamartoma. The histology of the "breast tumor" mentioned by patient No. 10 is unknown, but the patient is alive and well eleven years after the lesion was removed. The osteochondroma which developed in case No. 16 may have been related to the surgical treatment of congenitally dislocated hips. The cyst in the neck reported by patient No. 12 apparently developed after a blow and histologically consisted of chronic inflammatory tissue and old blood pigment. The "ovarian tumor" mentioned by patient No. 14 has not been reviewed but was removed along with the right tube, ovary and appendix and the patient is alive and well six years later. Patient No. 18 developed a mass along the right side of the sternum at twenty-two years of age and this was excised and proved to be a chondroma. Later the same year, this patient developed a carcinoma of the cervix which was shown to be intraepithelial. The details of the lesions developed by patients No. 17 and 19 are lacking. Both have recently been in the service and

are currently alive and apparently well.

Of the 867 patients whose thymic region was irradiated and upon whom follow-up information is available, 5 have subsequently developed a malignant neoplasm. Two of these lesions, the astrocytoma of the cerebellum and the carcinoma *in situ* of the cervix, are most probably not related to or associated with the previous radiation treatment of the thymic region. The other 3, the leukemia, the lymphosarcoma and the carcinoma of the thyroid may be. The summary of dosage and technical factors used in the irradiation of the thymic region in these 3 patients is:

Subsequent Malignant Neoplasm	Age When Irradiated	kv.	Field Size	Dose (Air)	Age When Developed Neoplasm
Leukemia (male	10 da.	150	10×10 cm.	200 r	5 yr.
Lymphosarcoma (male)	10 da.	150	10×10 cm.	200 r	9 yr.
Carcinoma of Thyroid (male)	2 mo.	200	10×10 cm.	150 r	9 yr.

It is not definitely known whether or not the patients who died of leukemia and lymphosarcoma had any other radiation treatment elsewhere although this seems unlikely. The mother of the patient with carcinoma of the thyroid was specifically asked about this possibility and remembered no other radiation treatment.

DISCUSSION

The observed occurrence of malignant neoplasms including lymphoblastoma and carcinoma of the thyroid in the patients whose thymic regions were irradiated at the University Hospital from 1932 to 1951 has been described. The interpretation of these findings and the discussion of their significance are in part speculative and it must be recognized that certain medical and statistical assumptions must be made in order to compare these findings with those reported by others. We are concerned primarily with the possibility that the previous irradiation of the thymic region may increase the likelihood of developing certain types of malignant disease. There has been an increasing amount of suggestive evidence that there is a correlation between radiation treatment of the head, neck, or chest of an infant or child and the subsequent development of a malignant neoplasm. Since we know what has occurred in this group of 867 patients who were irradiated for what was thought to be thymic enlargement, we would like ideally to compare this occurrence, this incidence of malignant neoplasms, to what has happened to a similar group of patients who were thought to have thymic enlargement but who were not irradiated. No such comparison is possible because we have no such group available to study nor has one been reported to our knowledge. There may be those who feel that since there are no known reliable measures of lymphoblastoma or carcinoma of the thyroid in such an untreated group there is no valid basis of comparison for the group we have studied. However, we feel that it may be informative to make some assumptions and attempt to determine what might be exexpected in a group the size and age of the one we have studied and observed over a similar period. We must realize that in doing this our conclusions can be tentative only. Simpson and Hempelmann[7] attempted to establish a basis for comparison of the group they studied by using a group of 1,933 untreated siblings as a control. They found that in this group no cases of lymphoblastoma or of carcinoma of the thyroid developed. The incidence of malignant disease they observed in their treated group was then compared to this control.

Another method of attempting to determine what the expected occurrence of lymphoblastoma or of carcinoma of the thyroid would be for a group of this size, of this age, and observed over this period of time is to use vital statistics rates and other sources

of information on the incidence of so-called spontaneous disease of this nature for the general population on the various age groups. These rates are determined from groups which may well include a few cases that had received radiation treatment of the thymic region, but the numbers of such cases are probably insignificant. Using the vital statistics rates,[8] the age distribution of our study population and the time of observation, it can be shown that the expected incidence of leukemia and lymphosarcoma for our group might be about 0.67 cases. This figure is in general agreement with the incidence for this age group reported by others.[4,5,9] Since we observed 2 cases of this type of malignant disease when we might have expected 0.67 cases, we are interested in testing to see if this difference is significant or whether it could have occurred by chance sampling alone. By using a significance test based upon the Poisson distribution, it can be shown that $P = 0.15$ which indicates that the event we observed could happen upon chance alone 15 times out of a 100.* We do not interpret this as being significant and conclude that the incidence of lymphoblastoma in our group seems higher than we might expect but not to a statistically significant degree.

The occurrence of carcinoma of the thyroid in children is a rare event. In 1955 Winship and Chase[10] reported only 285 cases having ever been published in the United States, Canada and Western Europe. Even in the endemic goiter areas, the number of cases is small. The Tumor Registry of the University Hospital contains over 30,000 patients and only 22, aged sixteen or under, are patients with carcinoma of the thyroid. None of these happens to be included in this study. The incidence rate shown in "Morbidity from Cancer in the United States"[6] among whites under twenty-five years of age is estimated to be about 0.5 per 100,000. For our group adjusted for its age distribution and observed over about 15,500 patient years, we might expect about 0.059 cases, slightly more than one-twentieth of a case. Since we have observed one case, have we a statistically significant difference in incidence? Again applying a significance test using the Poisson distribution we find that $P = 0.058$, which we interpret as indicating that the incidence of carcinoma of the thyroid in our group is probably significantly higher than might be expected.

Simpson and Hempelmann[7] reported 7 cases of leukemia and 10 cases of carcinoma of the thyroid out of their traced group of 1,502 patients. This represents a considerably higher incidence than in our group for both malignant diseases. Review of the dosage used for the irradiation of the thymic region of the cases of carcinoma of the thyroid they reported indicates that it was higher in all cases where the treatment factors were known than the dosage of radiation used in our single case of carcinoma of the thyroid. This is suggestive of a quantitative correlation between dosage of radiation to the thymic region and incidence of carcinoma of the thyroid. The dosage used in the 7 cases of leukemia reported by Simpson and Hempelmann is somewhat higher in 5 than in the 2 cases of lymphoblastoma we are reporting but this does not appear to be an important difference. More definite understanding of this correlation will depend upon studies of other groups and the evaluation of the combined results.

The occurrence of the other types of neoplasm, the osteochondromas and chondromas and the brain tumor, is interesting and the bony lesions arising in the area irradiated may have some relationship to the ionizing radiation, but without more accurate data for comparison little can be stated about the relative incidence. It should be noted that Simpson and Hempelmann[7] also encountered these types of neoplasms in their study.

The mechanism whereby the irradiation of the thymic region is perhaps conducive to the development of a malignant neoplasm five to ten years later is still obscure.

* We wish to express our appreciation to Mr. Fred Ederer, Mathematical Statistician, and Mr. Sidney J. Cutler, Head, End Results Evaluation Section, CCNSC, National Cancer Institute, Bethesda, Maryland, for their guidance and assistance in the statistical analysis of these data.

The possibilities include a latent effect on the bone marrow and thyroid gland directly or a hormonal effect due to the induced dysfunction of the thymus gland. Since so little is known about the normal role of the thymus and its relation to and influence on other organs and systems, further speculation seems premature.

SUMMARY

From 1932 to 1951 the thymic region of 958 patients was irradiated at the University Hospital. The dosage used was relatively low. Information on the subsequent course of 867 is known. Of this group 99 are dead. Two patients developed a lymphoblastoma, one, leukemia and one, lymphosarcoma. This incidence of lymphoblastoma is somewhat higher than might be expected but not significantly so. One patient developed thyroid carcinoma which constitutes a statistically significant increase in the expected incidence rate. These findings are further suggestive evidence of some increase in the incidence of neoplasia after the irradiation of the thymic region.

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THE SIGNIFICANCE OF THE TUMOR BED REACTIONS IN THE RADIATION TREATMENT OF MALIGNANT TUMORS*

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THE relative significance of the direct effects on the tumor cells and the indirect action mediated through the tumor bed is difficult to establish in clinical radiation therapy, and experimental studies are therefore required.

Suitable animal tumors similar to human cancers in histology, biologic behavior and radiation response have been difficult to find. Mammary cancers originating spontaneously in inbred strains of mice have been found to fulfill some of the criteria for an acceptable test object. Large numbers of identical tumors can be obtained by transplantation since the genetic material of each individual animal approaches in similarity that of identical twins. Thus tumors transplanted from one individual to another should grow and behave biologically almost like metastatic tumors in the original host.

The histologic picture of these tumors varies but can frequently be recognized as a type of adenocarcinoma with different rates of growth and degrees of differentiation. Spontaneous regression is practically never observed, and, if a careful technique is used, tumors almost always develop at the site of transplantation. The tumors grow until they ulcerate, become infected or metastasize and the host succumbs.

The advantage of using these animals and isologous tumor transplants is related to the fact that the radiation effects directly on the tumor and indirectly on the tumor bed can be studied both separately and concomitantly.

The disadvantage is related to certain doubts as to the applicability of conclusions derived from such experiments to human tumors. Some of these doubts originated before the importance of the genetic factors was clearly understood and immunogenetic responses led to an unstable tumor-host relationship. But even with the highly inbred strains available today, there are certain findings which indicate that a transplanted and a spontaneous tumor respond differently to treatment. It has been shown for instance that certain chemotherapeutic agents are effective in transplanted but not in spontaneous tumors in the same strain of mice.[21] There is apparently still some instability in the tumor-host relationship, which is most marked shortly after the transplantation when the tumor cells are still devoid of circulation before the capillaries of the host tissues proliferate and furnish blood supply to the tumor transplant.[11] Similar unstable relationships between the tumor metastases and the tissues into which they are implanted may exist under certain circumstances in the human.[4]

HISTORIC BACKGROUND REGARDING RADIATION STUDIES ON THE TUMOR BED IN MICE

In 1914 Frankl and Kimball[6] reported that there was "a powerful influence from irradiation of the tumor bed, resulting in an indirect influence on the growth of the tumor, indirect because the tumor transplant was never hit directly by the radiation." They worked with a mammary carcinoma which had been transplanted in mice for five years. The genetics of these mice were unknown. Five experiments with 12 mice in each were described. Six of the 12

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mice in each experiment were given a single roentgen ray exposure to either the entire back or to a local area on the back. The remaining 6 mice were kept as nonirradiated controls.

The dose of radiation was expressed as 50×, which resulted in partial epilation but no severe skin changes. The focal skin distance was 18 cm. Three millimeter aluminum filter was used but the kilovoltage was not stated. The radiation was probably relatively soft.

A previously transplanted tumor was dissected and the tumor cells suspended in Ringer's solution; the concentration was not specified. The cell suspension was then injected in volumes of 0.2 ml. (presumably subcutaneously) into the back a short time after the irradiation. The same volume of tumor cell suspension was injected into the nonirradiated control mice and all of them developed tumors which grew to a large size and killed the animals within a month. Three of the 6 irradiated mice failed to develop tumors; in 2 mice a small tumor developed but then regressed to a necrotic mass. In the sixth animal a tumor developed and grew slowly until the animal died after two months. The time of observation was apparently limited to two months, although this was not specifically stated. In all the other four experiments similar results were recorded.

The inhibitory effect on the growth of transplanted tumors by local irradiation of the tumor bed has been confirmed by many other workers.[1,12,13,15,20,22,24]

The mechanism of this effect has been assumed to be related to an alteration of the nutritional supply either qualitatively or quantitatively. Merwin *et al.*,[14] using the Algire transparent mica chamber technique and *in vivo* microscopy, obtained evidence to suggest that irradiation reduced the capacity of the capillary endothelium of the host to form buds to supply the implanted tumor fragments with blood. A dose of 2,000 to 3,000 r of roentgen rays caused a delayed circulatory block, and, as the tumor transplant slowly overcame this block, the vessels extending into it no longer exhibited the innumerable arborizations seen in nonirradiated control animals. The vessels therefore remained quite sparce and the growth of the tumor was inhibited. The question might be raised as to whether this effect could explain the observations of tumor cells lying dormant in irradiated tissues for months and years.

OUR EXPERIMENTS

Since most of the previous studies on the radiation effects on the tumor bed had been carried out with animals of unknown genetic constitution and often without exact specification of dose and physical factors of radiation, it was decided to repeat the experiments with inbred strains of mice and carefully controlled radiation factors.[22,26,27]

Material. The mice and mammary tumors were originally obtained from J. J. Bittner and in the earlier studies offspring of F_1 hybrids backcrossed to their Z strain parents (ZBC) were used as recipients for the tumor transplants. In later studies Z mice bred by brother to sister mating in our laboratories and breast tumors originating spontaneously in these mice were employed. Only male mice were used for transplantation.

Technique of Transplantation. The tumors were dissected out with sterile instruments, crushed in a tissue press and the pulp suspended in sterile 0.85 per cent NaCl. The tumor tissue suspension was mixed and diluted to 0.2 to 0.5 gm. per ml. and from 0.025 to 0.1 ml. of the cell suspension was injected subcutaneously on the ventral side of both hind legs with a 22 gauge needle pointed toward the ankle of the mouse. In other experiments only one leg was injected. Both the irradiated and the untreated control mice were injected simultaneously with the same cell suspension. The animals were examined once or twice a week, death rates were recorded and the growth rates of the tumor transplants were estimated by caliper measurements. Histologic examinations were carried out in parallel experiments (Fig. 1, *A* and *B*).

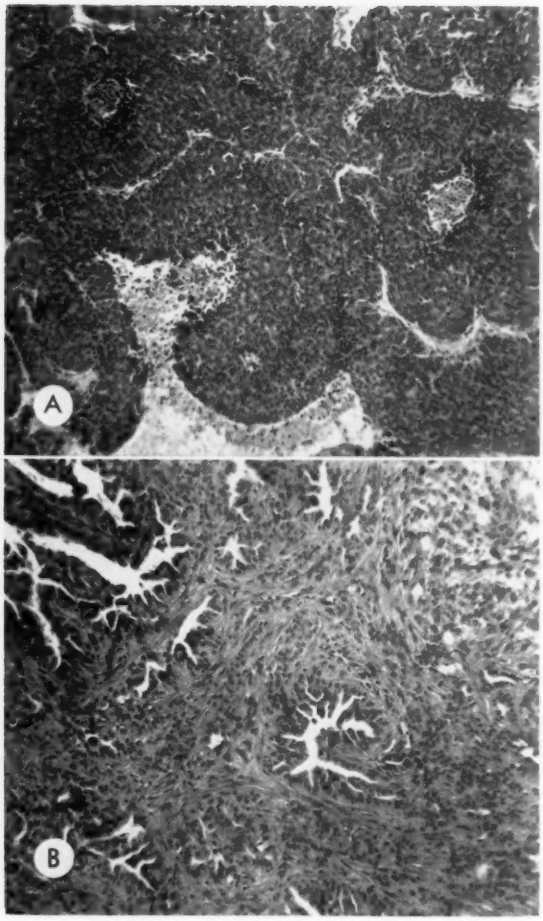

Fig. 1. (*A* and *B*) Histologic structure of two of the transplanted tumors used in these experiments.

Technique of Irradiation. Ten mice were mounted in a lead cylinder designed to allow local irradiation of one hind leg with a low simultaneous dose to the rest of the animal body. This lead cylinder could be screwed in position on a General Electric roentgen-ray machine which would be operated at 140 kv. with 20 cm. focal skin distance and 2 mm. of aluminum filtration. This gave a half value layer of 0.17 mm. of copper. The dose rate was 120 r/min. and was measured with a Victoreen r-meter with the thimble placed in the same position as was occupied by the hind leg of the mouse. On another machine with a slightly different geometric arrangement, the dose rate was 144 r/min.

RESULTS

(a) *Pretransplantation Irradiation.* In all mice receiving radiation to the leg before the transplantation of fresh nontreated tumor (pretransplantation irradiation), the tumor growth was retarded. The most pronounced effect was obtained in the ZBC mice receiving tumor transplants on both the shielded and the irradiated leg. Even after a relatively small dose of roentgen rays (1,500 r in air) to the tumor bed, a marked difference in the size of the tumors on the two legs could be demonstrated (Fig. 2). Similar results were obtained in a total of 10 experiments with 20 mice in each, 10 irradiated and 10 controls. The tumors on the shielded leg grew at the same rate as in the nonirradiated control mice. In 21 of 55 animals which survived six weeks, no tumor could be palpated on the irradiated leg. The remaining 34 mice had small tumors which grew slowly in the irradiated tissues. All 55 mice had large ulcerating tumors on the shielded leg at the end of six weeks.

In subsequent experiments the tumors were transplanted only to the right leg and the growth rate of the tumor could be determined over a longer period of time. The growth pattern of any one of the transplanted tumors varied considerably, but during a certain period it seemed to be characterized by a relatively constant rate of volume increase. This seemed to be true for the tumors growing on an irradiated leg as well as for the controls, the only difference being that the growth rate was reduced in the irradiated animals. An increase in the time interval between the transplantation and the appearance of a palpable tumor nodule was observed after irradiation. The animals which had received pretransplantation irradiation lived longer than their nonirradiated counterparts. The optimal dose producing the longest average survival was 3,000 r (Fig. 3). After twelve weeks the mice in this group also began dying and after twenty weeks very few survived. The gain in the average length of sur-

Fig. 2. Ten mice were given 1,500 r in air to the left hind leg. Forty-eight hours later nonirradiated fresh tumor tissue suspension was injected subcutaneously into the irradiated area. Serial photographs show the inhibition of tumor growth six weeks after the transplantation. All the control mice had large ulcerated tumors on both legs.

vival amounted to 5.7 weeks (irradiated $13.8 \pm .42$, control $8.1 \pm .32$, $K = 10.7$, $P = 0.0001$).

Most of these experiments were carried out with purebred Z mice and tumors originating spontaneously in Z females were used for transplantation. The data show that pretransplantation irradiation did not prevent transplanted tumors from developing in this strain even though there was a significant delay and retardation of their growth and prolongation of life of recipient animals. In many of the animals the tumors grew outside the irradiated leg and infiltrated the tissues in the inguinal region.

In a study using radioactive phosphorus as a tracer, the turnover of desoxyribonucleic acid (DNA) in these tumors was determined. The technique has been described elsewhere.[28] The data are given in Table 1.

It was unexpected to find that the uptake of P^{32} into the DNA was not significantly lowered in spite of the reduced growth rate of tumors growing on an irradiated tumor bed. The data suggested that DNA can be synthesized at normal rate even though the tumor growth is markedly retarded.

(b) *Post-transplantation Irradiation.* A study of the relative effects of irradiation before and after the transplantation of tumor was also carried out on purebred Z strain mice and tumors.

The first striking finding was the marked radioresistance of the established mammary carcinoma in this strain. Similar results had been reported by others.[8,9,25] A dose as high as 6,000 r in one single exposure failed to eradicate the tumor when administered

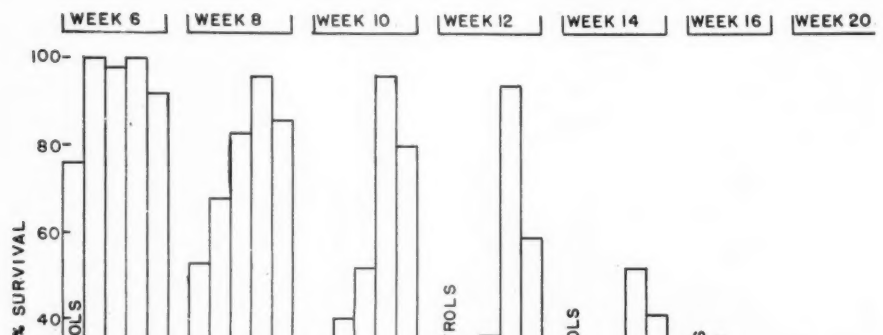

FIG. 3. One single exposure of local roentgen radiation to one leg followed by injection of nonirradiated fresh tumor tissue suspension forty-eight hours later.

TABLE I

EFFECT OF PRETRANSPLANTATION IRRADIATION ON THE UPTAKE OF P^{32} INTO DNA OF MOUSE MAMMARY TUMORS

Roentgen-Ray Dose 4,500 r in air; Time between P^{32} Tracer Study and Sacrifice: One Hour

Interval between Transplantation and P^{32} Tracer Study	Irradiated		Controls	
	Tumor Weight	Relative Spec. Activity	Tumor Weight	Relative Spec. Activity
42 days	0.30	0.69	2.62	1.05
	0.65	1.30	1.16	1.24
	1.16	1.16	0.48	1.14
	0.34	1.08		
	0.30	0.97		
	0.22	2.05		
56 days	0.50	0.78	2.50	0.76
	1.00	0.67	4.30	0.80
61 days	0.20	1.12	1.90	0.99
	0.50	0.77	2.40	0.92
74 days	0.70	0.64	0.50	0.75
82 days	0.50	1.08	4.50	0.76
Mean	0.53	0.92 ±SE* 0.18	2.26	0.93 ±SE* 0.04

* SE = standard error.

more than three weeks after the transplantation, when most of the tumors could be palpated as distinct nodules.

Complete or almost complete regression usually occurred after this dose, but in a group of 30 animals all developed recurrence in the treated area a few weeks later. All of these mice died with large tumors (Fig. 4). Actually the average survival of the mice which were irradiated more than three weeks after the implantation of tumor was similar to that of mice given pretransplantation irradiation using the same dose levels.

Quite a different picture emerged, however, when the roentgen treatment was given a shorter time after the transplantation. Marked delay or even complete inhibition of the growth of the tumor transplant occurred when the leg was irradiated two weeks or a shorter time after the transplantation. This effect was demonstrable with a dose of 1,500 r. Thus, in an experiment with 20 mice receiving immediate post-transplantation irradiation, only 10 developed tumors during a period of observation of more than one year. In the re-

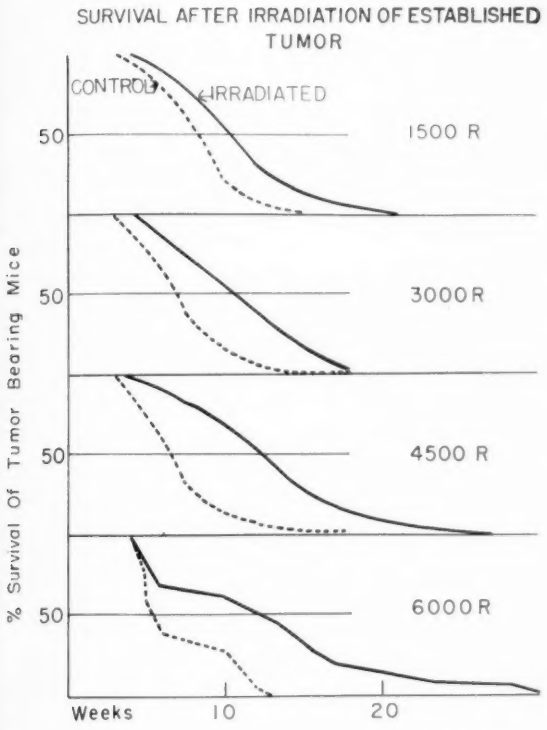

FIG. 4. Mammary tumors were transplanted into one hind leg and irradiated when the tumor was readily palpable as a distinct nodule more than three weeks after the transplantation. Each experimental group had at least 30 animals.

maining 10 the tumors grew slowly after a long latent period. All the control mice developed tumors and died within three months.

A study of the effects of larger doses of roentgen rays given either before or after the transplantation is illustrated in Figure 5.

A dose of 4,500 r resulted in an average length of survival of 44.2 weeks when delivered shortly after the transplantation. Almost as good results were obtained when the roentgen treatment was given seven days after the transplantation; but irradiation three weeks after the transplantation gave about the same survival as with pre-transplantation irradiation.

The data on the tumor incidence in animals observed more than one year after the treatment showed that slightly more than 20 per cent of animals treated within two days after the transplantation developed tumors. When the delay between transplantation and irradiation was increased to

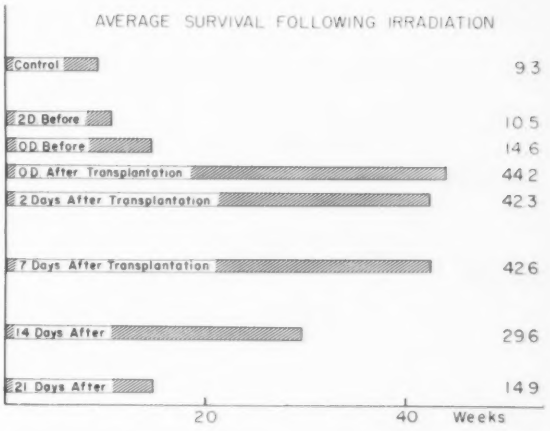

FIG. 5. Eight groups with 10 mice in each were treated with 4,500 r in air either before or after the transplantation of tumor. They were then observed until they died.

two weeks, the tumor incidence was slightly over 50 per cent. All of the control mice developed tumors (Fig. 6).

In a group of 70 mice irradiated within two weeks after the tumor was transplanted, 48 mice failed to develop tumors over a period of more than one year. Their life span was increased to close to the average for mice without tumors. In 20 of the 70 mice (32 per cent) tumors developed at the site of the inoculation but only after a long period of latency during which time the tumor cells lay dormant in the irradiated tissue. In a few animals this latent period lasted more than a year. Thus, in 10 of the 22 mice with tumors, the tumor

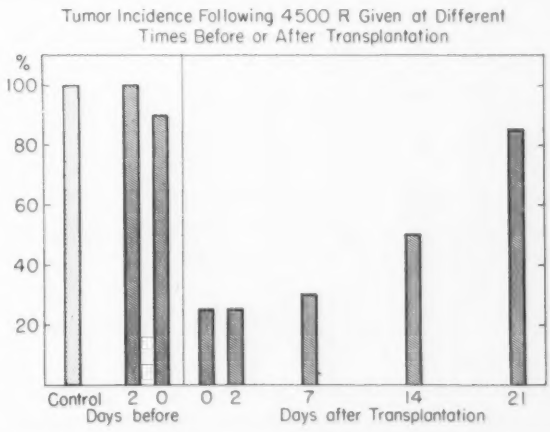

FIG. 6. Tumor incidence recorded after observing the animals over their entire life span.

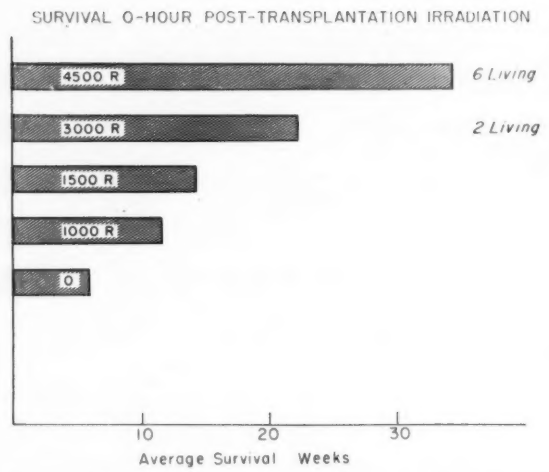

FIG. 7. Mice in groups of 10 each were irradiated immediately after the tumor transplantation.

nodule did not become palpable until between forty-six and seventy-five weeks after the transplantation. Once established, the tumors grew rapidly even after this long latent period, and the mice were usually dead within three to five weeks after the tumor had become palpable.

In the group of mice which were irradiated immediately after the transplantation, there was a decreasing incidence of tumor development and an increasing length of survival of the animals with increasing dosage of roentgen rays up to 4,500 r (Fig. 7 and 8).

In a group of animals which had received tumors which had been transplanted for

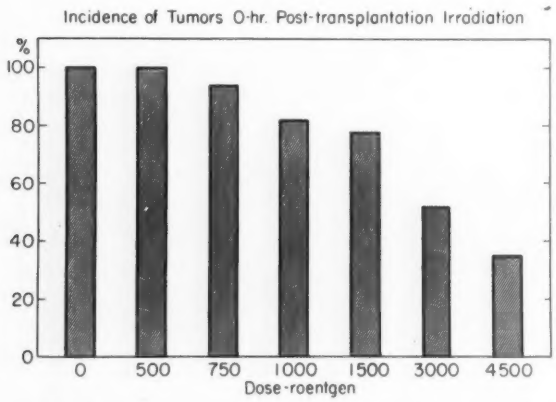

FIG. 8. Mice in groups of 10 each were irradiated immediately after tumor transplantation and observed until death.

nearly twenty generations, the effects of both pre- and post-transplantation irradiation were reduced. Such tumors acquired greater malignancy with marked increase in the growth potentials.

(c) *Irradiation of Tumor Cell Suspensions in Vitro.* In order to throw further light on the tumor bed response, experiments were carried out to compare the effects of irradiation of tumor cells outside the animal body with the results from irradiation of the tumor bed.

A transplanted tumor was dissected out and divided into two equal parts and cell suspensions were prepared in two separate glass beakers. One beaker was immediately irradiated inside the lead protective device in the same position used for irradiating the legs of the mice. The other beaker was kept at room temperature outside the room. The thickness of the fluid level was about 1 cm. Immediately afterwards, the irradiated cell suspension was injected into nonirradiated Z male mice. Mice of the same age, sex and strain had received 3,000 r to the right leg forty-eight hours before and nonirradiated tumor suspension was then injected into

TABLE II

EFFECTS OF IN VITRO IRRADIATION OF TUMOR SUSPENSION COMPARED WITH PRETRANSPLANTATION IRRADIATION OF THE TUMOR BED

Roentgen-Ray Dose 3,000 r in air; 10 Mice in Each Group

Experiment	Tumor Transfer	Average Survival after Transplantation in Weeks ± Standard Error		
		Controls	Tumor bed	In vitro
1	X_2	7.3±0.1	9.5±1.8	12.8±1.0
2	X_3	8.2±1.5	10.8±1.3	15.6±1.7

COMPARISON BETWEEN TUMOR BED AND IN VITRO IRRADIATION

Experiment	Difference between the Means	K	P
1	3.3 weeks	1.6	0.1
2	4.8 weeks	2.2	0.03

the irradiated tissue. Nonirradiated control mice were injected with the same suspension. The results are shown in Table II.

Thus *in vitro* irradiation is slightly more effective than pretransplantation irradiation but is far inferior to post-transplantation irradiation given within two weeks after the transplantation.

Similar results have been reported by Goldfeder.[9] The results suggest that there are factors in the host which contribute to the radiation effects on the transplanted tumor cells. However, because the cell suspension irradiated *in vitro* was not saturated with oxygen, it is possible that hypoxia might have played a role in producing apparent resistance to radiation.

DISCUSSION

It is commonly assumed that the effects of ionizing radiations on malignant tumors are due to the absorption of radiant energy and the resulting chemical changes within the malignant cells. Thus the cells of certain radiosensitive tumors (*e.g.*, seminomas, neuroblastomas, leukemias and some of the lymphosarcomas) disintegrate, apparently as a result of a direct action initiated by the ionization within their boundaries.

Experience with clinical radiation therapy has clearly indicated, however, that the condition of the tissues in which the tumor grows, the tumor bed, may modify the response to radiation.[18] It is understandable that the tumor bed should be of some significance because the tumor depends on the nourishment supplied by the surrounding tissues. Oxygen, amino acids, carbohydrates, fatty acids, vitamins, minerals, and hormones are important metabolites necessary for the anabolic chemical reactions which lead to growth and reproduction of the tumor cells and these metabolites have to be transported through the tumor bed. The vascular as well as the cellular reactions in the tumor bed signify its participation in the over-all radiation response. Therefore, a tumor bed which is well vascularized is usually considered more favorable for radiation therapy than one which is relatively avascular. The therapeutic ratio is increased because of the better potentials for healing and the greater radiosensitivity of the cancer cells. This may explain why the results of radiation therapy of facial skin cancer are better than those obtained in histologically similar tumors of the skin of the ear, neck, hands and trunk and why lymph node metastases are often more resistant than the primary tumor.[23] Tumors developing in previously irradiated tissue, scars and old fistulous tracts are notoriously difficult to eradicate with irradiation.

Other well known environmental factors influencing the radiocurability of malignant tumors include tumor infiltration of bone or cartilage, infection and anemia, all of which tend to worsen the prognosis. Tumors transplanted into rats which were fed a protein deficient diet showed high incidence of recurrence after radiation treatments, but regressed permanently in 90 per cent of the irradiated animals when the rats were maintained on a diet with high protein content.[3]

The poor results of radiation therapy of carcinoma of the esophagus, hypopharynx, bronchus, and intestines may be related to the unfavorable tumor bed.

Large tumors are frequently more difficult to cure by radiation therapy even though the histologic picture may be similar to that observed in a smaller more radiosensitive tumor.[17]

There is a possibility that many of the observations may be explained as due to a relative hypoxia or anoxia in certain parts of the tumor.[10] The lack of oxygen in the cells may change the biologic effectiveness of the radiation by altering the pathways of transfer of radiant energy in water. In the presence of oxygen the free radicals found in the intracellular water enter into reactions which, according to present hypotheses, result in an accumulation of highly reactive oxidizing compounds or molecular fragments (OH, HO_2, H_2O_2). Interaction between these and intracellular enzyme systems may lead to disturbance of the in-

termediary metabolic reactions which normally funnel energy into the biochemical synthesis of cell constituents necessary for growth and cell division. In the absence of oxygen the radicals tend to recombine and become inactive before interacting with the organic compounds of the cell.[2]

Other observations point to biologic mechanisms which are yet poorly understood. There are certain similarities between the tumor bed response in radiation therapy[5] and the changes seen after successful hormone therapy in breast cancer. Histologic studies reveal a relative increase in the fibrous stroma associated with a decrease in the number of tumor cells.[16] These changes may be interpreted as reflecting an augmented resistance in the tumor bed as the stimuli for tumor growth are counteracted or lacking. The attenuation of the tumor cells by the direct radiation effect has allowed the defense mechanisms of the tumor bed to become mobilized sufficiently to prevent the growth of the tumor cells. There is also ample evidence to indicate that such defense barriers may be broken down at a later date permitting recrudescence of the tumor.

The data presented regarding decreased length of survival of patients treated with supraoptimal doses of radiation[19] may be interpreted in light of the tumor bed defense response. Excessive doses may break down the regenerative capacity of the tumor bed and residual cancer cells may proliferate unhampered by the defensive barriers created with optimal dose levels.

SUMMARY

1. Inbred mice of the Bittner Z and ZBC strains have been used to study the effects of roentgen radiation on transplanted mammary carcinoma and the tumor bed.

2. Irradiation of the tumor bed before transplantation of fresh untreated tumor resulted in retarded tumor growth and delayed onset of palpable tumor nodule. The irradiated animals lived longer than the unirradiated controls but irradiation of the tumor bed alone did not prevent the tumors from growing and all the mice eventually died with large tumors. The dose which caused the optimal effect was 3,000 r.

3. Irradiation after the transplantation with dose levels up to 6,000 r failed to eradicate the tumors when the time interval between the transplantation and the roentgen treatment was more than three weeks.

4. Irradiation within two weeks after the transplantation resulted in permanent inhibition of the tumor growth in close to 70 per cent of the animals. In the remaining 30 per cent, the tumors developed after a long latent period which in some mice extended over more than one year.

5. Tumors growing slowly in an irradiated bed showed similar uptake of radioactive phosphorus into the desoxyribonucleic acid isolated from the tumors as found in the nonirradiated controls.

6. Irradiation of tumor tissue suspended in physiologic saline *in vitro* failed to prevent tumor growth upon subsequent transplantation into nonirradiated animals and was less efficient than *in vivo* roentgen treatments given a short time after the transplantation. *In vitro* irradiation was slightly more efficient than roentgen treatment of the tumor bed in inhibiting tumor growth.

7. In view of these experimental data, the significance of the tumor bed and the host reactions in radiation treatment of malignant tumors have been discussed.

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THE COMBINATION OF OXYGEN AND OPTIMUM FRACTIONATION IN RADIATION THERAPY OF ADENOCARCINOMA*

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THE increased effectiveness of radiation in the presence of oxygen has been known for a long time. This fact has been used to explain the clinical observation that tissues with a normal blood supply are more radiosensitive than those lacking it. Large tumor masses are thought to be more radioresistant than small ones because of the decreased blood supply in their centers. The possibility of using oxygen to increase tumor response in clinical radiation therapy has been discussed many times and is now under trial in a number of radiation therapy centers.

This study is mainly concerned with the effect—if any—of oxygen on optimum fractionation. The term "fractionation" is sometimes used in the literature to denote protraction of the over-all time of irradiation, but it is used here to mean the breaking of the total dose into fractions, or the dose and timing of the individual treatments.

In an earlier study[1] it was shown that when spontaneous mammary adenocarcinoma in C_3H mice is treated at the rate of 2,000 r (air) per week to totals of 6,000 r or 8,000 r the response is better when treatment is given three times a week rather than daily (five days a week). The larger the individual dose the longer is the interval required between treatments for better response. Oxygen renders the dose more effective and might therefore require lengthening of the time between treatments. It was, then, proposed to repeat the same techniques while the mice breathed oxygen, to determine whether the difference in tumore response would still be observed.

Hollcroft and co-workers[4] showed that transplanted lymphosarcoma in mice regressed more rapidly after a single irradiation in a high oxygen atmosphere than in air or low oxygen atmosphere. This was confirmed by Lanier and co-workers[5] for daily treatment of transplanted mammary tumors in mice. This would not necessarily be true for spontaneous tumors, at least to the same degree. Gray[3] has pointed out that the improvement in response for a given increase in oxygen concentration is greater when the initial concentration is low. Spontaneous tumors have a better blood supply than transplanted tumors and therefore might not show the response to the addition of oxygen evident in transplanted tumors. Furthermore, the goal of radiation therapy is complete disappearance of the tumor. As Glucksmann[2] says, "A 90 per cent success of therapy is ultimately a failure" and "Decrease in tumour-volume of itself is no real measure of the efficiency of therapy." Actually, the curves of Hollcroft *et al.*[4] show the high oxygen tumors outstripping the others in rate of regrowth. Therefore, the criterion of response in the experiment reported here is that there be no evidence of tumor on palpation.

All details of the supply and handling of the mice were the same as in the earlier experiment[1] with the exception of the animal room. The new, permanent quarters are air-conditioned to keep the temperature and humidity constant and more precautions are taken against the introduction of infections. Their value was demonstrated on two occasions when a four-fold increase in the number of mice dying on one day

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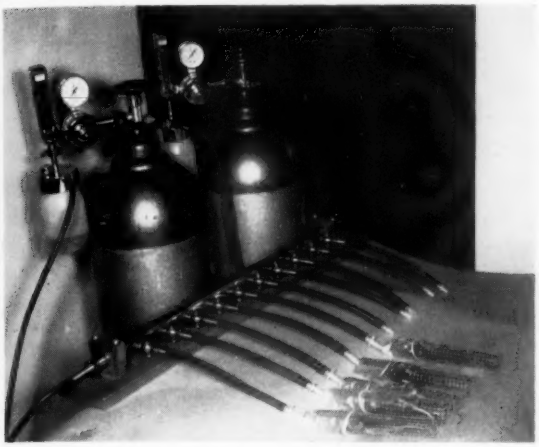

Fig. 1. Mice receiving preradiation oxygen.

was explained by a change of six degrees, lasting about two hours, shown on the constant recording temperature chart.

Previous experience with these C3H mice had convinced us that it would be impractical to attempt to use oxygen pressures of three atmospheres or more to obtain higher oxygen tensions, as is done in some radiation therapy centers. The two experiments already cited were done at atmospheric pressure, Hollcroft *et al.*[4] allowing the mice to breathe 95 per cent oxygen and 5 per cent carbon dioxide for a few minutes before and during treatment and Lanier *et al.*[5] using pure oxygen for half an hour before and during treatment.

In the first part of our experiment the mice breathed 95 per cent oxygen and 5 per cent carbon dioxide for half an hour before and during treatment. This is available for general hospital use and is obtained from commercial distributors. If each mouse were handled separately, there would be a delay of at least thirty minutes before the next mouse could be started. To prevent this delay, during the preradiation period a manifold with ten stopcock-controlled outlets along its length was used (Fig. 1). Each end was connected to a G tank of the gas mixture with an atmospheric reducing valve and a humidifier which contained distilled water to reduce the dryness of the mucous membranes of the respiratory tract. A latex hood or sleeve was used to envelop each mouse and its wire holding-jacket. The rate of flow of the gas was 3 to 5 liters per minute per mouse. It was evident that each mouse was receiving an adequate supply of gas by the ballooning of the hoods. Between the hood and the manifold was a plastic male-female connector. This facilitated easy and rapid movement of the mouse from the room where it received its preradiation gas mixture to the treatment room. In this room a similar G tank was used with a single tube connection for oxygen administration during treatment. The effects of the carbon dioxide were manifest within seconds after breathing it by hyperventilation, shortly followed by redness of the paws as a result of the systemic vasodilatation.

The results of treatment for this group of mice are compared in Figure 2 with those for the mice treated previously without oxygen. In every instance the results are improved by the addition of oxygen. The advantage of treating three times a week with these doses is still evident, however. The best results of all are obtained by the combination of oxygen and optimum fractionation.

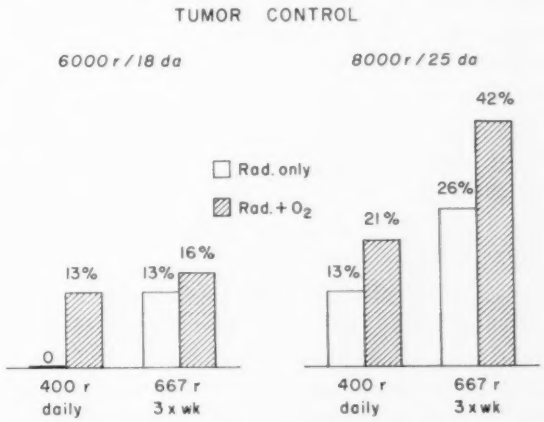

Fig. 2. Per cent of mice which completed treatment and showed no evidence of tumor on palpation. (There were between 30 and 40 mice in each group, a total of 268 mice.)

Mean tumor diameters

With oxygen 14.7 mm. Without oxygen 13.0 mm.
3 times a week 13.8 mm. Daily treatment 14.0 mm.

Statistical significance (ΣX test of Cochran)

Oxygen plus radiation versus radiation only $p = .01$
Three times a week versus daily treatment $p = .002$

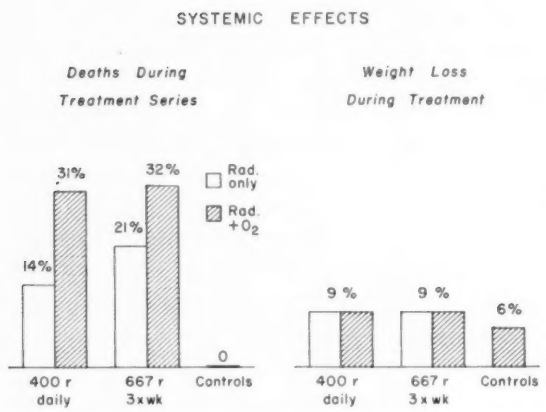

FIG. 3. Comparison of systemic effects on mice treated with radiation only and with radiation plus oxygen-carbon dioxide. (There were 70 to 115 mice in each group; p = .001.)

As always, the value of a therapeutic technique depends on its differential effect on tumor and normal tissues. Referring again to Gray,[3] failure to control a tumor can be due to the presence within it of small anoxic regions in which the radiation is relatively ineffective so that viable cells remain from which the tumor regenerates. A uniform increase in oxygen supplied to all tissues should have a greater effect in these regions, with consequent improvement in the differential.

Subjectively, no difference in skin reactions could be seen. This would be expected because of the good initial oxygen supply of the skin. A comparison of systemic effects with and without oxygen is not quite valid since the two series were not simultaneous, although they did overlap somewhat in time. However, all techniques were repeated over a period of a year or more and this should eliminate many variables. In addition, all changes, such as conditions in the animal room, skill of handling, etc., favor the oxygen series. In spite of this (Fig. 3) the number of mice dying before completion of the treatment series was increased by the addition of oxygen. Weight loss during treatment showed no increase. Control mice subjected to the same handling and breathing the gas mixture for the same length of time, but not irradiated, showed almost as much weight loss, but no deaths. This has led to the conclusion that weight loss is not a good index of the comparative morbidity of these techniques since for all of them the loss approaches the critical value for survival. Mice suffering greater damage are automatically eliminated from weight loss data by death and appear only in the mortality data.

This finding of increased systemic effect seemed important enough for further investigation. A new group of mice was treated with 6,000 r in twenty-five days with treatment being given at increasing intervals. Part of these mice breathed the gas mixture for half an hour before and during treatment, and part started breathing it just before treatment. Tumor response (Fig. 4) was essentially the same in both groups, which agrees with the work of others who have shown that the increased radiosensitivity occurs almost immediately after the introduction of oxygen. The number of deaths, however, was considerably reduced by eliminating the half hour of preradiation breathing of the gas. This result, together with the weight loss of those mice receiving the gas mixture without irradiation, makes it apparent that part of the sys-

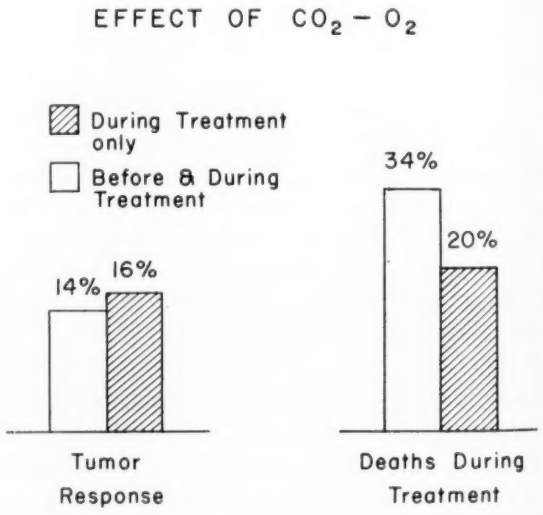

FIG. 4. Effect of breathing the gas mixture for half an hour before treatment. (There were 44 mice in each group.)

temic effect is due to the gas itself. In view of the extreme sensitivity of these mice to any trauma, it seems possible that the hyperventilation induced by the carbon dioxide, together with the chemical changes in the blood and the toxic effect of the oxygen, might explain these results. Further investigation of this problem will be made to determine the relative importance of the two gases in producing this systemic effect and also in controlling the tumor response. At any rate, it is obvious that, under these treatment conditions, the time of breathing the gas should be as short as possible, and this means making the treatment time short.

The report of Lanier and co-workers[5] shows that tumors in mice breathing oxygen grow slightly faster than those in the control mice and, as was already mentioned, the curves of Hollcroft *et al.*[4] show that high oxygen tumors out-stripped the others in rate of regrowth. In both cases the effect was too small to be significant, but, because of its occurrence in both studies and particularly because of the importance of its application to clinical radiation therapy, it was thought worthwhile to examine our data for this effect. If oxygen were to cause undetected or known metastases to grow more rapidly during treatment of the primary tumor, its value as an adjunct to radiation therapy would be questionable, at least.

In order to check this aspect of the use of oxygen, the number of additional tumors developing during treatment, and presumably due to growth of tumors too small to detect at the beginning of treatment, was compared for the groups with and without oxygen (Fig. 5). In both groups it was 11 per cent. Furthermore, it would seem that if oxygen is responsible for the appearance of these tumors, the mice breathing oxygen for half an hour before treatment should develop more tumors than those breathing it only during treatment; the mice treated (and receiving oxygen) daily should show more tumors than those treated (and receiving oxygen) only three times a week;

TUMORS APPEARING DURING TREATMENT

With Oxygen 11%	
Before and during treatment 18%	During treatment only . . . 19%
Daily treatment . . . 5%	Treatment 3 times a week . 12%
25 day treatment . . 6%	18 day treatment 10%
Without Oxygen 11%	

Fig. 5. Incidence of new tumors during treatment.

and, finally, treatment for four weeks should result in more tumors than treatment for only three weeks. Actually, the differences shown here are in every case in the opposite direction from that to be expected if oxygen stimulates tumor growth. Again the differences are not statistically significant and the conclusion from all three experiments could be that oxygen has no effect. There is another possibility, however. The increased rate of growth shown by Lanier *et al.*[5] was for oxygen alone, without radiation. It has been shown[6] that rats with two transplanted tumors showed regression of the untreated tumor when one tumor was irradiated. It may be that the explanation for our results is that the inhibiting effect of the radiation is greater than the stimulating effect of the oxygen, under these treatment conditions.

It would seem from these results that oxygen can be a two-edged sword and should be used with caution in clinical radiation therapy. The possibility of stimulation of untreated metastases should be considered, if the "balance of power" is disturbed. Patients should be watched carefully for untoward systemic reactions. Nevertheless, it seems possible that oxygen, even at atmospheric pressure, may offer a means of improving clinical results. This procedure is practical in any radiation therapy department. The value of optimum fractionation should not be lost sight of, however, since this can also improve re-

sults, and, judging by this experiment, to about the same degree.

SUMMARY

The results of irradiating spontaneous mammary adenocarcinoma in C3H mice at the rate of 2,000 r per week to totals of 6,000 r or 8,000 r can be improved by allowing the mice to breathe 95 per cent oxygen and 5 per cent carbon dioxide during treatment; however, the advantage of breaking the total dose into fractions given three times a week as compared to daily treatment is still apparent. Although skin reactions appear to be the same, systemic effects, as measured by number of mice dying before completion of the treatment series, are increased by the gas mixture. These can be minimized by keeping the time of breathing it as short as possible.

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The authors wish to express their appreciation of the technical assistance of Henry Taylor in treating the mice.

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IMMEDIATE POST-EXPOSURE PERMEABILITY CHANGES, AND SOME LATER RESPONSES, OF MAMMALIAN SKIN X-IRRADIATED WHILE ANOXIC AND AT DIFFERENT TEMPERATURES*

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BY REASON of limitations attaching to available techniques, the elucidation of the physiopathology of radiation injury is at present largely limited to indirect approaches.[8] Such approaches involve the study of factors that are calculated to modify the response of a protoplasmic system to ionizing radiation. One of the most important of these response-modifying factors is temperature. Temperature changes in living systems may, for reasons of convenience, be equated with changes in metabolic rate.

It is generally acknowledged that the course of radiation-induced injury is dependent on the temperature prevailing after the period of irradiation. Reduced temperature following exposure is accompanied by retardation or postponement of visible expression of injury while heightened temperature following exposure is accompanied by accelerated and enhanced manifestation of damage. However, information relating to the question of the influence of temperature *at the time of irradiation* can only be characterized as conflicting and equivocal. In reference to this issue, Patt and Brues[6] have well said that " . . . virtually every conceivable effect has been described." The biologic and physical factors involved in such studies are so varied that there appears to be little prospective gain in attempting to classify or reconcile the observations.

The present study is concerned with certain phases of the problem of the role of temperature at the time of irradiation, as a dose-effect modifying factor, in x-irradiated mammalian skin, specifically the rabbit ear. It has been known for many years that reduced temperature in mammalian skin, during exposure to roentgen rays, is accompanied by reduced radiosensitivity. This has been interpreted in terms of the accompanying reduction in vascular supply. In turn, the radiosensitivity-modifying effect of changes in vascular supply has been ascribed to the consequent alterations in oxygen tension. In effect, the protective influence of cooling during irradiation has been attributed to the anoxic condition it promotes.

However, more recently it has been demonstrated (in the rabbit ear) that the temperature prevailing in *anoxic* mammalian tissue at the time of irradiation is a significant dose-effect modifying factor.[4] When skin areas are rendered anoxic by mechanical compression and simultaneously irradiated under different temperature conditions, the cooled area suffers significantly less damage. This throws new light on the problem of the manner in which temperature at the time of exposure affects the response of mammalian skin to ionizing radiation.

Generally speaking, under the circumstances of the work cited above,[4] the first evidence of biologic response to the radiation is an erythema appearing two to three hours after irradiation. This erythematous condition is reflected in a hyper-reddening

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of the irradiated area as a result of the dilatation of the capillaries and their distention with blood. (Historically speaking this was probably the earliest recognized biologic response to roentgen rays.) The interval between the irradiation and the appearance of the erythema has traditionally been known as the latent period. This term is unsatisfactory, for, most certainly, rather than being a period of "latency," it is a period during which extremely important changes are occurring. To designate it as the period of "dark reactions" or "obscure reactions" would seem preferable. It is with events occurring during this period that this investigation is chiefly concerned.

It has already been shown[4] that from the first appearance of the radiation erythema to eight weeks following irradiation the successive responses of cold-irradiated (10°C.) and warm-irradiated (39°C.) anoxic rabbit skin are distinctly different. These studies were not, however, designed to reveal any differences in cold-irradiated and warm-irradiated areas during the so-called latent period.

In view of the fact that the severity of the post-latent period manifestations of damage are characteristically different in cold-irradiated and warm-irradiated anoxic skin areas, it is reasonable to assume that some difference also prevails during the latent period. It is another thing to demonstrate this. Histologic studies at this stage are not calculated to be of much help.[1] Rather, some less equivocal, functional criterion of differential-response is needed. Accordingly, since changes in permeability characteristics are generally regarded as among the very earliest biologic responses to roentgen rays, it was decided to employ this as a criterion of damage. As a means of detecting any differences in permeability characteristics during this period, trypan blue, to be injected intracardially following irradiation, was selected. This vital dye has been widely used in studies on inflammation and radiation damage; its localization in inflamed or irradiated areas is taken as an indication of increased permeability in such regions and this, in turn, is regarded as a manifestation of injury.[7]

The specific aim of this study is, therefore, to ascertain whether a differential manifestation of radiation injury, in terms of altered permeability, can be detected during the interval commonly termed the latent period in areas of rabbit skin exposed to roentgen rays while anoxic and respectively cooled and warmed during irradiation.

MATERIALS AND METHODS

New Zealand white, virgin female rabbits of 4–5 pounds were employed. Some twelve hours prior to experimental manipulation, the ears were shaved with a surgical clipper; this reduces absorption of radiation by extraneous hair and facilitates observation. Immediately prior to experimentation the animals were anesthetized by means of an intraperitoneal injection of veterinary sodium nembutal (Abbot).

The method by which anoxia (dehematization), temperature-regulation and irradiation of a localized area of the ear were simultaneously effected is portrayed in Figure 1. Cooling or warming is accomplished by a gravity flow of water of desired temperature through the hollow chambers. The compression weight on the ear areas totals 1,150 gm. The present device represents an important improvement over the method described earlier,[5] in that, here, temperature-regulation of a given area is effected by direct cooling or warming of both the dorsal and ventral surface. The beryllium compression surface insures maximum transmission of the soft x-radiation to the area in question (Fig. 2). It is important to emphasize (cf. Fig. 4) that the compressed (anoxic) area is of larger diameter than the irradiated area. This, it will be seen, allows control areas to be observed in one and the same experimental ear. The arrangement and dimensions of nonirradiated and irradiated anoxic areas, under different temperature conditions, are depicted in Figure 4. The temperatures of

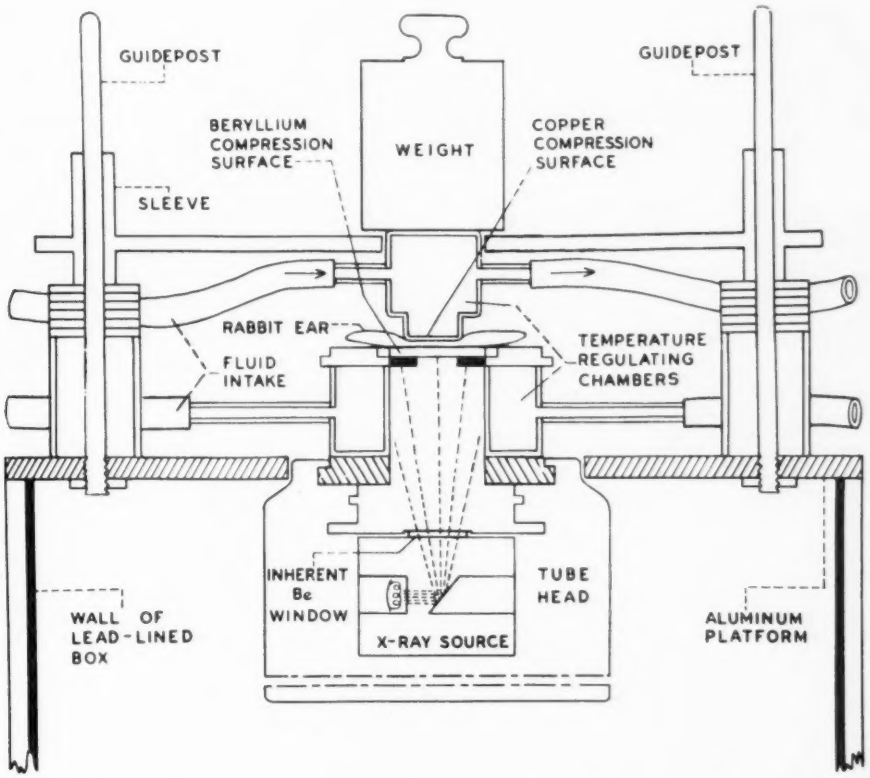

Fig. 1. Diagram of the experimental apparatus by means of which anoxia, temperature-regulation and irradiation are simultaneously effected in localized areas of the rabbit ear. This technique represents a significant improvement over a method earlier described by O'Brien *et al.*[4] in that in this situation the temperature-regulation of the anoxic area is effected by two metal surfaces, copper dorsally and beryllium ventrally; the latter greatly enhances the transmission of the soft x-rays to the tissue and provides more uniform and effective temperature-regulation (cf. Fig. 2).

the ear tissue areas were determined by means of a thermocouple. The temperatures to which the ear areas were subjected were 3° or 9°C. and 39° or 45°C. Since the results are essentially the same using either of the lower or either of the higher temperatures, the temperature situation will hereinafter be referred to simply as cooled or warmed.

By employing a tandem arrangement of copper temperature-regulating chambers (Fig. 3), it proved convenient to accomplish the simultaneous irradiation of an anoxic area on each of the ears of a single animal, one area being cooled and the other warmed during exposure. One disadvantage of this method is the necessity of reducing the size of the dehematized and irradiated areas in order to maintain the same target-tissue distance. Another is the fact that here temperature-regulation must be limited to the upper surface. In these experiments (tandem arrangements), however,

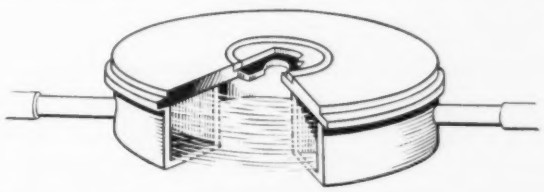

Fig. 2. A cut-away drawing of the device by means of which temperature-regulation of the beryllium compression surface (ventral) is accomplished (cf. Fig. 1). The beryllium disk is uppermost in the center of the chamber, within which flows water of any desired temperature; the beryllium surface assumes the temperature of the circulating water within 0.3°C. This arrangement insures uniform warming or cooling of the anoxic tissue areas and also allows for greatly enhanced transmission of the soft radiation to these areas.

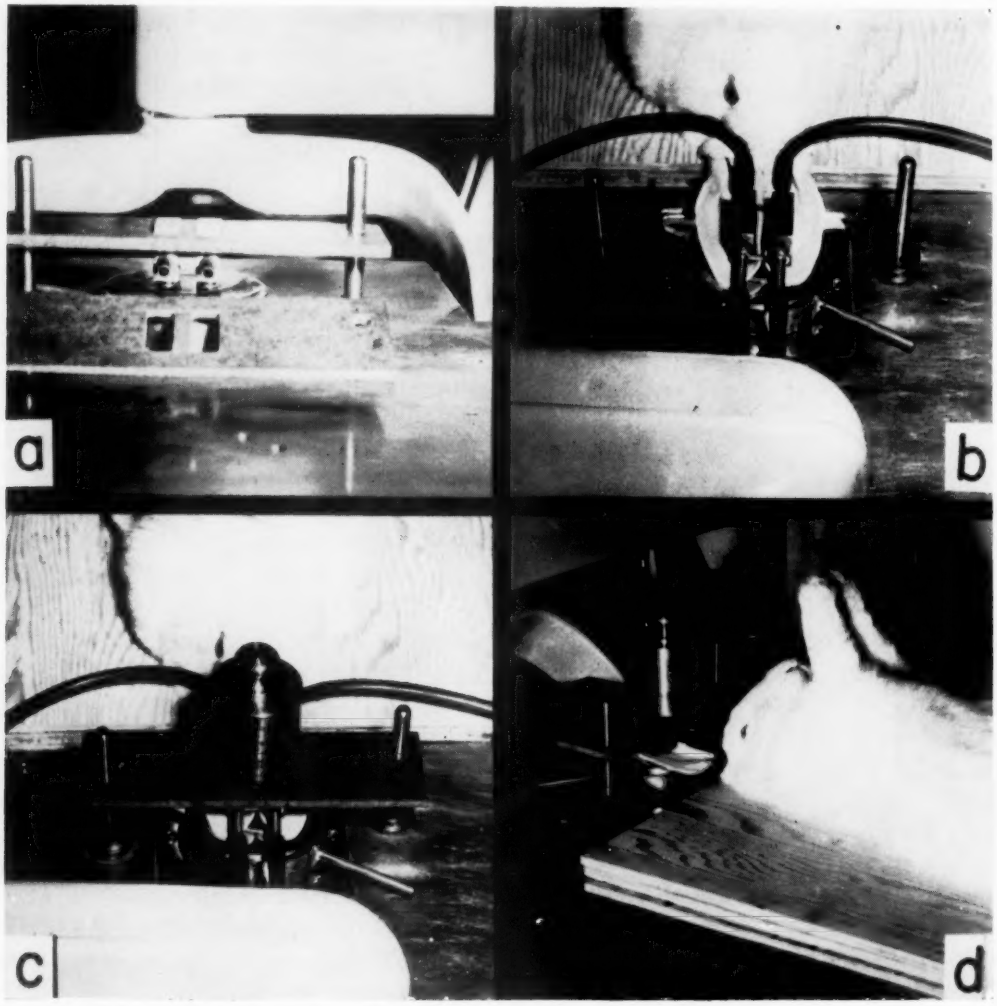

Fig. 3. Arrangement employed for effecting simultaneous irradiation of a cold and warm area in, respectively, the left and right ear of a single animal. (*a*) Tandem arrangement of anoxic-inducing and temperature-regulating chambers resting on a beryllium compression surface. (*b*) Rabbit ears and chambers in place. (*c* and *d*) Two views of completed arrangement with 1,000 gm. weight in place. (Temperature-regulation from the dorsal surface only in this arrangement.)

the results are essentially the same as when single exposures are made, at different times, on the ears of different animals. In Figure 3 several views of the employment of this tandem arrangement are presented.

The timetable of experimental manipulations principally employed in this study was as follows: (a) three minutes of compression only (dehematization), with a view to utilization of residual oxygen in tissue to be irradiated; (b) five minutes of continued compression with temperature-regulation, with a view to effecting the desired skin temperature before start of irradiation; (c) twelve minutes of continued compression and temperature-regulation in addition to exposure to x-radiation; (d) cessation of irradiation and immediate release of ear areas from compression and temperature-regulation; (e) intracardial injection of trypan blue, within two minutes of completion of step (d). Observations on any localization of trypan blue in the experimentally-altered ear areas, and the relative rate and total intensity of such localization, were recorded (photographically) at appropriate intervals up to one hour following injection of the dye.

Radiation conditions. GE Maximar 100 unit; 50 kv.; 5 ma.; 3,200 r/min. (measured

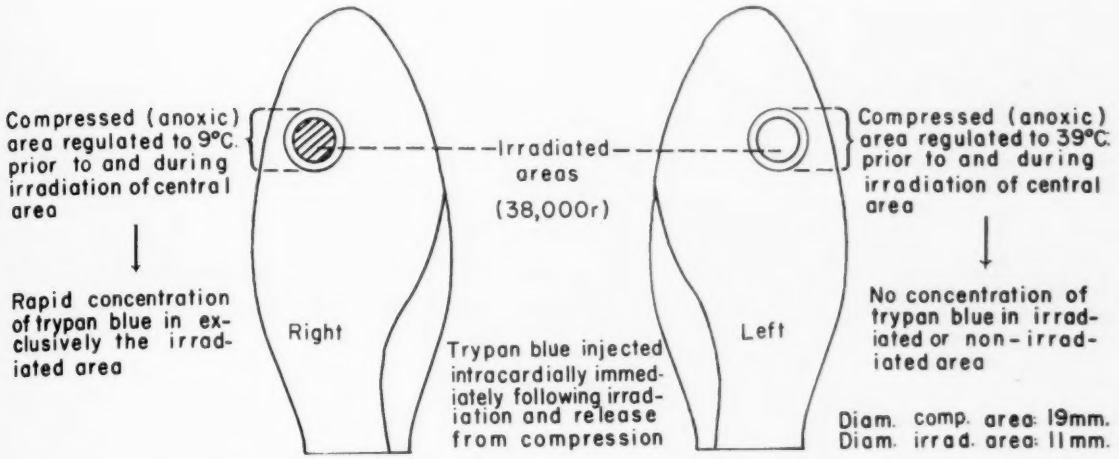
Compressed (anoxic) area regulated to 9°C. prior to and during irradiation of central area
Irradiated areas (38,000r)
Compressed (anoxic) area regulated to 39°C. prior to and during irradiation of central area
Rapid concentration of trypan blue in exclusively the irradiated area
Right
Trypan blue injected intracardially immediately following irradiation and release from compression
Left
No concentration of trypan blue in irradiated or non-irradiated area
Diam. comp. area: 19mm.
Diam. irrad. area: 11mm.

FIG. 4. Summary diagram of the conditions and results of the principal experiment. The irradiation of the cooled and warmed areas may be effected on separate animals or simultaneously on a single animal; results are the same in either case. It is important to realize that while an area (19 mm. in diameter) is compressed and regulated to one or other temperature, only the central portion thereof (11 mm. in diameter) is irradiated; this allows experimental and control areas to be observed in one and the same ear.

in air at beryllium compression surface); total dose, 38,400 r.*

Trypan blue (Harleco "Parstains") was employed in the form of a 1 per cent aqueous solution; single injections of 5 cc. were made into one or the other ventricle. Care was exercised to ensure that the entire 5 cc. of dye was injected into the ventricular cavity.

In order to answer certain supplementary questions relating to the principal issue engaged, additional experiments were performed in which the timetable of experimental operations (particularly the post-irradiation conditions) differed from that described for the principal experiment. It will be most convenient to characterize these different questions and their experimental implementation in their proper places below.

OBSERVATIONS

The observations recorded here will, for convenience, best be divided into two categories: (1) those relating to what will subsequently be referred to as the principal experiment and (2) those relating to such supplementary experiments as were designed to clarify the results of the principal experiment.

THE PRINCIPAL EXPERIMENT

The question to which this experiment was directed is: Taking the intensity of deposition of trypan blue in irradiated areas as a criterion, is there manifest any differential alteration of permeability characteristics during the so-called latent period in areas of rabbit skin x-irradiated while anoxic but respectively cooled or warmed during exposure? Details of the experimental procedure and timetable have been described above.

Of eight ear areas irradiated while anoxic and cold, all exhibited an early, rapid, and intense localization of trypan blue immediately after irradiation. Of five areas irradiated while anoxic and warm, none exhibited any localization of trypan blue. The non-irradiated control areas, simultaneously subjected only to anoxia and cooling or warming, exhibited no localization of trypan blue. The results of this experiment are diagrammed in Figure 4, and a series of photographs showing this localization of trypan blue in the cold-irradiated area, as seen at different intervals following intracardial injection of the dye, is presented in Figure

* We have been asked the reason for our employing such a heavy dose. We arrived at this empirically; we found[4] that the saving effect of reduced temperature in anoxic skin during irradiation was most strikingly demonstrated with a dose of radiation of this magnitude.

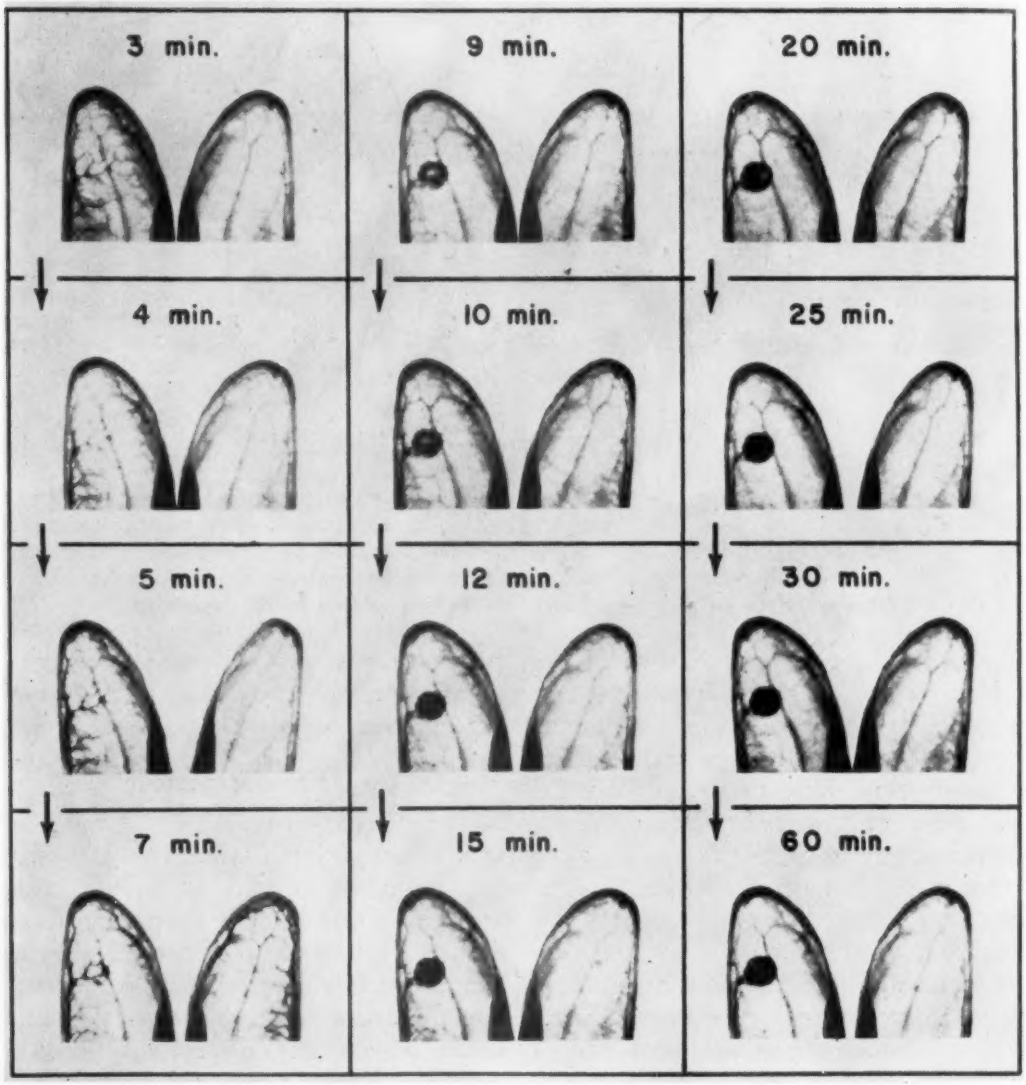

Fig. 5. Progressive accumulation of trypan blue in cold-irradiated areas as seen at different time intervals following post-irradiation intracardial injection of the dye. While no area of the ear at right was irradiated in this particular animal, it presents, subsequent to injection of the dye, the same picture as an ear area irradiated while warm. The *ultimate* damage is characteristically and significantly less in the areas irradiated while anoxic and cold.[4]

5. The thirteen areas to which reference is made above were on thirteen different rabbits.

These results indicate that localization of trypan blue occurs only in areas of rabbit skin in which anoxia, temperature-reduction, and irradiation have been effected *simultaneously*. For reasons to be discussed later, it may be said that this is a decidedly unexpected finding. In order to secure further assurance that this differential localization of trypan blue occurs only when anoxia, temperature-reduction, and irradiation are effected simultaneously, several supplementary questions were posed and experiments calculated to answer them performed.

THE SUPPLEMENTARY EXPERIMENTS

While the indicated questions might be formulated in theoretical language (say, in terms of permeability change, injury, re-

covery, etc.), it was judged that such would lead to unwarrantedly complicated formulations by reason of the multifaceted character of the several situations. Accordingly, they are formulated, largely, in simple empirical language. These questions do not represent all the possible variations that could be suggested, but we believe they are calculated to provide solid assurance that the major indication, deriving from the principal experiment, is correct.

(1) *What effect would a delay in the injection of trypan blue have upon the localization of the dye in the cold-irradiated areas?* In the course of preliminary studies, it appeared that a delay in the injection of trypan blue after exposure had an important bearing on the localization of the dye in the cold-irradiated areas. In an effort to learn more about this, the usual procedure of the principal experiment was followed except that injection of the dye was delayed for twenty-five minutes following release of the ear areas from compression and temperature-regulation. Under these circumstances, no localization of the dye occurs in the cold-irradiated areas; neither does it occur in the warm-irradiated areas under otherwise similar circumstances.

The results of this experiment indicate that the increase in permeability in cold-irradiated ear areas, immediately following exposure, can be a very short-lived phenomenon. This apparent cancelling-out of the permeability change (by merely waiting twenty-five minutes before injecting the dye) is difficult to understand; it suggested, however, that perhaps the same reversal might be achieved by immediate, experimentally-enforced post-irradiation warming for only a very few minutes. This is the point of the following question and experiment:

(2) *Will rapidly-induced post-irradiation warming, for two to five minutes, affect the originally noted localization of trypan blue in cold-irradiated anoxic skin areas?* The basic procedure and timetable were again employed; however, instead of releasing the ear areas immediately after exposure, postirradiation warming was effected two to five minutes before mechanical release and injection of trypan blue. The rapid warming was effected by changing the temperature of the circulating water in the temperature-regulating chambers immediately after irradiation. The localization of trypan blue in cold-irradiated areas, warmed for two to three minutes after exposure, was greatly reduced in intensity; the first faint localization of dye occurred four to five minutes after its injection. When the warming period was extended to five minutes, there was either no localization of the dye or only a barely perceptible one (Fig. 6). These results demonstrate that increased temperature after exposure definitely contributes to the "cancelling-out" of the early increased permeability observed in cold-irradiated areas during the latent period.

This remarkable increase in permeability in cold-irradiated areas is further emphasized by the fact that if the dye is injected for as long as thirty minutes prior to the irradiation and mechanical release of such areas, it will nevertheless concentrate heavily in the cold-irradiated area. This is depicted in Figure 6. The above results suggested a consideration of the effect of extended cooling (following irradiation) of cold-irradiated and warm-irradiated areas; accordingly, we addressed ourselves to the following two considerations:

(3) *Does extended cooling following irradiation affect the localization of trypan blue in cold-irradiated areas?* The basic procedure and timetable were employed but instead of releasing the cold-irradiated areas immediately after exposure, compression and cooling were continued for an additional twenty to thirty minutes, following which trypan blue was intracardially injected. Under these circumstances, the cold-irradiated areas exhibited localization of the dye that was in no way distinguishable from that which occurred in the principal experiment. These results demonstrate that continued cooling (beyond irradiation) issues in the persistence of this increased permea-

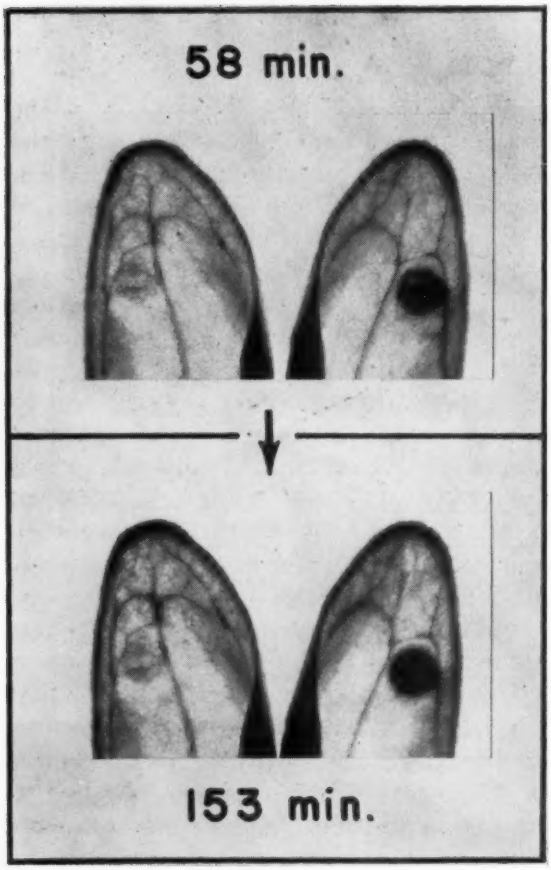

Fig. 6. Ear at left exhibits a very faint localization of dye, as seen at two intervals following its injection, in a cold-irradiated area *subjected to post-exposure warming for five minutes*. The brief post-irradiation warming period has in some way "reversed" the dye deposition phenomenon depicted in the other ear (cf. Fig. 5 also). Ear at right exhibits a conspicuous localization of dye in the cold-irradiated area (opposite ear of same animal) not subsequently warmed but released immediately after exposure. These particular ear areas were not irradiated simultaneously. A single injection of trypan blue was given immediately after the five minute warming of the area to the left; the warming was done some thirty minutes before completion of irradiation and release of the area to the right.

bility. It is important to recall that when such an area is allowed to warm up naturally for twenty-five to thirty minutes following mechanical release—or when the warming up is induced in the area for five minutes subsequent to the irradiation (before release)—the permeability change is no longer evident. Clearly, it is not the time (*per se*) elapsing between the irradiation and the injection of the dye that is important in the persistence or "cancelling-out" of this permeability change; rather, it is the temperature prevailing after exposure that is important. This led us to a further question.

(4) *Will immediate post-irradiation cooling of warm-irradiated areas result in the localization of trypan blue?* Since the principal experiment demonstrated that reduced temperature and irradiation, simultaneously effected, are accompanied by localization of trypan blue, it appeared conceivable that reducing the temperature to such an area immediately after exposure might result in localization of the dye in such areas. The basic procedure and timetable were again followed, but instead of releasing the warm-irradiated area immediately after exposure, cooling was effected for five or seventeen minutes; then the area was released and trypan blue injected. No localization of trypan blue occurred in areas so treated.

Taken singly and cumulatively the results of these supplementary experiments support the indication, deriving from the principal experiment; namely, that localization of trypan blue occurs *only when chilling and irradiation are effected simultaneously*. In addition, these experiments demonstate that this increased permeability is short-lived and can be eliminated by postexposure warming; however, it persists with continued postirradiation cooling.

DISCUSSION

The results of these experiments demonstrate that in anoxic rabbit skin, reduced temperature at the time of exposure to soft x-rays causes an immediate and remarkable increase in permeability; this can be experimentally eliminated by postirradiation warming (rapid or slow) but is not affected by continued postirradiation cooling. On the other hand, in anoxic skin subjected to warming during irradiation, there is no such manifestation of increased permeability; nor does such occur even when

warm-irradiated skin is subjected to reduced temperature immediately after exposure.

In view of the fact that the skin areas irradiated while anoxic and at the higher temperature ultimately exhibit significantly greater damage than comparable areas irradiated while anoxic and cold,[3] it seemed reasonable to anticipate that if any significant alterations in permeability were to be detected during the "latent period," they would be reflected in the warm-irradiated areas. But, as has been shown, they are not.

It is difficult to see how this dye deposition phenomenon in the cold-irradiated areas could be regarded as an expression of the saving effect of reduced temperature during irradiation; it is no less difficult to see how the nonoccurrence of the dye deposition in warm-irradiated areas can be regarded as an expression of greater radiosensitivity of the tissue area involved. This early and striking localization of trypan blue is certainly not a reliable criterion of over-all primary radiation damage.

It may be said that an important and largely neglected area of study in the clarification of the physiopathology of radiation injury lies in the detection of changes occurring *immediately after irradiation*. Next to the energy exchanges consequent upon the direct impact of the radiation insult on the protoplasmic system involved, these "dark reactions" may be reasonably regarded as the most significant. In a word, events of direct and momentous relevance to the particular syndrome of injury must occur during this period. The observations reported in this paper point up the fact that with suitable methods it is possible to detect changes occurring during this so-called latent period. But in the present instance these permeability changes are difficult to interpret.

Neither cooling nor irradiation alone is accompanied by localization of trypan blue under the circumstances of these experiments. Accordingly, any explanation of the phenomenon must include effects of the radiation and effects of the reduced temperature; for it is only when they are applied in combination that the localization of dye occurs. Yet, in view of the eventual fates of the cold-rradiated and warm-irradiated areas, this early differential response (in terms of changes in permeability) cannot be regarded as greater initial radiation-induced damage.

The unexpected concentration of trypan blue in the cold-irradiated area might be explained as follows: chilling results in the inhibition of some temperature-sensitive phase of one or more early chemical reactions precipitated by the radiation. In this view, the increased permeability is regarded as a consequence of the accumulation of some intermediate substance (s) which does not accumulate in the warm-irradiated area. This explanation with its hypothetical substance (s) is even more unsatisfactory when it is realized that it is hardly verifiable under the defined conditions.

Local nervous reactions and/or thromboses might also affect the localization of the dye in the cold-irradiated areas. Menkin[3] believes that: "local vasoconstrictor nerve reactions may be very important under the circumstances of these experiments." Capillary thrombosis might be enlisted as a contributing factor. For example, if thrombosis is severe in a warm-irradiated area immediately after exposure, entrance of the dye into this area would be mechanically prevented. These aspects of the problem remain to be investigated. Commenting on the results reported here, McCutcheon[2] found no satisfactory answer and does not believe there is one at the moment.

Taken at face value, the fact that the accumulation of the dye in the cold-irradiated area can be experimentally prevented merely by warming the area in question (quickly or slowly), subsequent to the exposure and prior to injection of the dye, would seem to indicate that this is an example of recovery (restoration) from radiation-induced injury.

As a final word it may be said that the type of observations reported here point up

the necessity of devising methods by which the very earliest radiation-induced changes can be detected and identified in biologic systems. The term "latent period" is misleading and (as many have suggested) might well be dropped from the language of radiation biology and medicine.

SUMMARY

A striking increase in permeability characteristics in rabbit skin, as reflected in localized accumulation of intracardially injected trypan blue, occurs immediately following irradiation of skin (ear) areas under conditions of simultaneously effected anoxia and greatly reduced temperature; no such permeability changes occur in skin areas similarly irradiated while anoxic but maintained at heightened temperature during exposure.

These permeability changes occur only when temperature-reduction and irradiation are effected simultaneously. These changes are experimentally reversible and it seems reasonable to regard this as an example of recovery (restoration) from radiation-induced injury.

The immediate increase in permeability characteristics, manifested in the cold-irradiated areas under the conditions of these experiments, is not a reliable criterion of over-all radiation damage, since such areas ultimately exhibit considerably less injury than comparable areas similarly irradiated while warm.

These results can be regarded only as highly unexpected and we are not able, at this time, to provide an explanation for the phenomena. These observations emphasize the importance of devising methods to detect changes occurring during the so-called latent period.

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DEPTH DOSIMETRY FOR 250 KV. PEAK ROENTGEN RAYS BY MEANS OF A GEL-INCORPORATED CHEMICAL SYSTEM*

By L. H. GEVANTMAN *and* J. F. PESTANER
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A DEPTH-DOSE distribution in dogs irradiated with 250 kv. peak roentgen rays was established recently,[1] using ion chamber measurements. The dose measurements were made during a bilateral exposure of a tissue-equivalent (Mix D wax) dog phantom in which the ion chamber was prepositioned. It was observed that the percentage of air dose values tended to drop slightly in going from the surface to the midline of the phantom. Although the bilateral exposure dose distribution is in many instances indistinguishable from that of a rotational exposure, there is some evidence that the latter yields a more uniform depth-dose curve.[3] Consequently, the present study has been initiated to measure the dose distribution of 250 kv. peak roentgen rays in a rotated dog phantom so that these results may be compared with the distribution found for the bilateral exposure. A chemical system of trichloroethylene dispersed in an agar gel was used.

EXPERIMENTAL

The gel dosimeter preparation, irradiation and subsequent analysis have been described previously.[2] The radiation source was a Westinghouse X-ray machine operated at a setting of 250 kv. peak and 15 ma., with 0.5 mm. Cu and 1 mm. Al filtration. The target skin distance (TSD) was 115 cm. Incident radiation flux was measured both with Victoreen ion chambers and ferrous sulfate dosimeters. The phantom exposure assembly is shown in Figure 1.

RESULTS AND DISCUSSION

The dose-yield relationship for the gel in the spectral region of interest was established in two ways. The first consisted of the unilateral exposure of a stationary 5 inch cube of Mix D containing a gel cylinder. The variation in yield of H^+ produced with depth was compared with the unilateral depth-dose distribution measured with ion chambers embedded at corresponding depths in the same cube. The second involved the exposure of individual slices of the gel, 5 mm. thick, for varying lengths of time. The relationship which evolved is shown in Figure 2, where the yield in micromoles of H^+ per liter is plotted against the dose in electron volts absorbed per gram. It is seen that the yield is linear with dose up to approximately 60 μM and then starts to bend over. The G_{H^+} (G is the molecules produced per 100 ev. absorbed) calculated for this linear portion of the curve gives a value of 269 ± 10. This is approximately twice the value obtained for a 50 kv. peak exposure[2] and indicates a corresponding sensitivity increase in the dosimeter system.

Another method which has been examined for use in measuring unilateral depth dose involves the use of the ferrous sulfate dosimeter. A polyethylene cylindrical plug, as shown in Figure 3, was made to replace the gel dosimeter plug in the cavity of the 5 inch wax cube. Each of the series of holes which had been drilled along its entire length normal to its longitudinal axis was filled with 0.5 ml. of ferrous sulfate dosimeter. The holes were sealed with polyethylene caps to eliminate evaporative losses. The plug was positioned in the cube and irradiated in a way similar to the gel dosimeter for two hours at 101.5 cm. TSD. Following irradiation, each sample was measured optically at 304 mμ. for the presence of ferric ion. The results which represent an average of 3 runs are given in Fig-

* From the United States Naval Radiological Defense Laboratory.

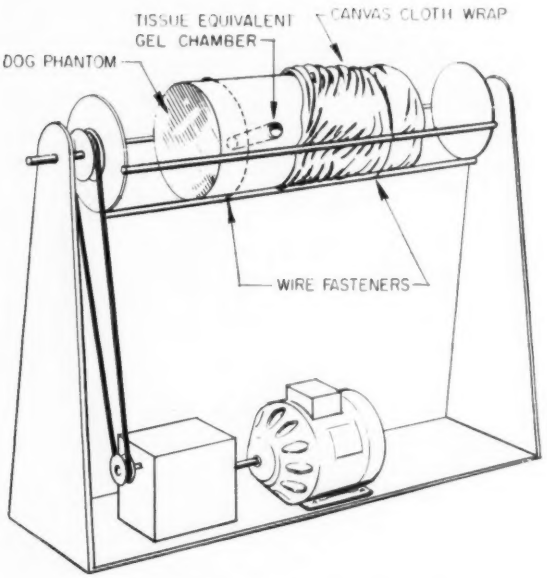

FIG. 1. Phantom exposure assembly.

ure 4, where they are compared with thimble chamber measurements made in the manner previously described.[2] The agreement is fairly good at the front end where a reasonable change in optical density has occurred. However, as the optical density changes decrease in going toward the rear of the cube, the spread in values goes as high as 10 per cent. Nevertheless, the system may be used to good advantage and, with some improvements, may be superior to ion chamber measurements in this energy region. It should be noted that this system does suffer the disadvantages of long exposure times as well as radiation conditioning of the polyethylene to a point where it does not interfere in the ferrous-ferric oxidation.

The depth-dose distributions obtained

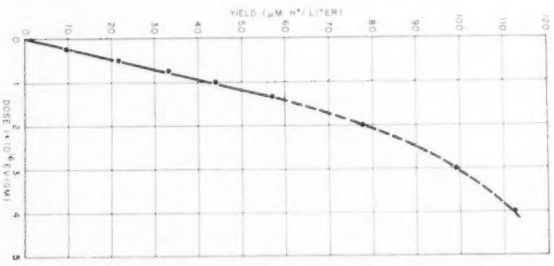

FIG. 2. Dose yield in gel for 250 kv. peak roentgen rays.

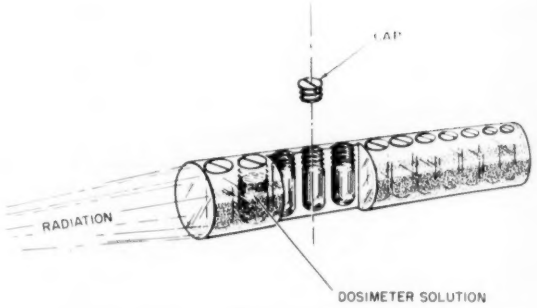

FIG. 3. Polyethylene plug for measuring unilateral depth dose with ferrous sulfate dosimeter.

with the gel dosimeter for both the unilateral and rotational exposure are shown in Figure 5. The uniformity in dose throughout the depth of the rotated phantom is immediately obvious, confirming the expected distribution differences between the rotated and bilateral exposure. The gradual drop in dose across the phantom is believed real and reflects the eccentricity in rotation of the phantom. The build-up shown in the unilateral curve by the ion chambers is larger than that shown by the gel and is closer to the value shown in the rotational distribution. Inasmuch as there is considerable difficulty in obtaining surface dose measurements with ion chambers, it is felt that a value of about 5 per cent is probably valid. This value also agrees with that of Alpen and Jones.[1]

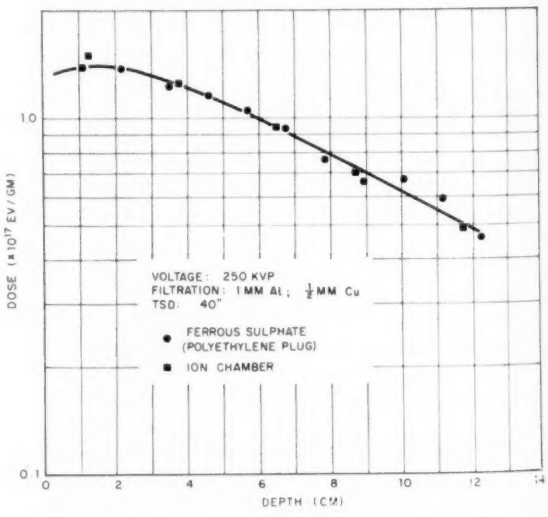

FIG. 4. Comparison of unilateral depth dose in wax phantom.

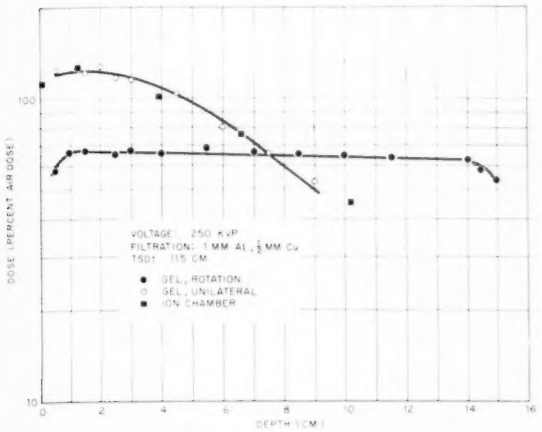

FIG. 5. Comparison of unilateral with rotational depth dose.

The internal reproducibility of ±3 per cent exhibited by the gel in the rotation experiment is quite good, although there may be a difference of ±5 per cent between gels. This does not alter the effect shown but does make its absolute value somewhat less exact. However, this does not make the method less useful since ion chambers will generally reproduce within this range.

CONCLUSIONS

The uniformity in dose across the dog phantom for a rotational exposure is confirmed. This is contrasted with the bilateral exposure which shows about a 10 per cent fall-off in dose at the midline. This serves to emphasize the efficacy of rotational over bilateral exposure when dose uniformity is desired. The usefulness of the gel dosimeter for measuring rotational depth-dose distributions is again demonstrated. The ferrous sulfate dosimeter shows some promise in measuring unilateral depth dose, but requires further development before it can become a preferred method of measurement.

SUMMARY

The method used to measure depth-dose distribution for low energy roentgen rays in a rotated dog phantom is employed in a similar measurement for 250 kv. peak roentgen rays. It consists of a chemical dosimeter (trichloroethylene) incorporated into a firm aqueous gel. The results show a slight rise in absorbed dose just below the surface, followed by a uniform dose throughout the rest of the phantom. This is contrasted with a bilateral exposure which shows a slight drop in absorbed dose at the center of the phantom.

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A NOMOGRAM FOR DOSAGE CALCULATIONS IN TELECOBALT THERAPY

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A NOMOGRAM has been devised to replace conventional depth dose tables and treatment time-dosage calculations in telecobalt therapy. This nomogram, as illustrated in Figure 1, enables one to obtain all physical factors with speed and accuracy while reducing the amount of arithmetic to a bare minimum. Changes in the output of the cobalt 60 unit are taken into account by adjusting the position of a movable index. This feature enables the same nomogram to be used over a period of years and even after a new source is installed. Separate nomograms are needed for each source skin distance utilized. The nomograms illustrated below were constructed with the aid of central axis depth dose data previously published by Johns.[1]

The development of the nomogram was accomplished in three separate stages. First, Johns' data were modified so as to give depth dose as percentage of air dose. These data were then plotted on linear paper with depth as ordinate and the percentage of depth dose, running from 0 to 105 per cent, as abscissa. Secondly, on the right hand side of the nomogram are given the values of roentgens per minute and divided into equal increments starting from zero and going to a value slightly higher than the present output in air. A movable index (a piece of string) is constructed so as to pass through the origin at the lower left hand corner and the point of intersection of the present output and 100 per cent depth dose lines. The results of this construction are shown in Figure 1 where 32 r/min. was the output of the telecobalt unit at the Montefiore Hospital at the time this paper was written.

At this stage in the construction, the depth dose as a percentage of the air dose and the roentgens per minute at the depth of interest can be obtained. The way in which this is done is illustrated by the dashed and dotted lines in Figure 1. The dashed line relates the depth of 6 cm. and the depth dose of 76 per cent for a 10×10 cm.^{2} field. The dotted line rises from the point of intersection on the depth dose curve until it meets the movable index. Moving horizontally to the right, we find the output at the 6 cm. depth to be 25 r/min.

The third step in the construction consists in relating treatment time and specified tumor dose. Across the top of the nomogram a time scale running from right to left is plotted. The position and dimensions of the time scale in relation to the other scales are not critical and should be chosen so that the specific tumor dose curve described below never becomes so steep as to impair the accuracy of the nomogram. A specific tumor dose curve is now constructed according to the equation

(Treatment Time in minutes) × (roentgens/minute at depth) = Tumor Dose

A separate curve for each tumor dose could be drawn, but it has been found that two, for 100 r and 150 r, are sufficient for practical purposes. Figure 2 illustrates this additional construction and, in relation to the example given above, shows how the treatment time necessary to give a tumor dose of 100 r is obtained. If a perpendicular line is erected starting at the intersection of the horizontal dotted line which indicates the roentgens per minute at the tumor and the specific tumor dose curve, it will meet the time scale and indicate the exact treatment time. This perpendicular line is drawn as a heavily dashed line in Figure 2.

Figure 3 illustrates a ready to use nomo-

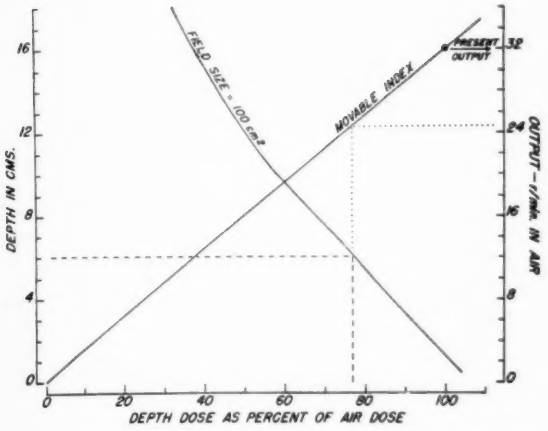

FIG. 1. Telecobalt nomogram for 80 cm. source skin distance. The first stage in the development of the nomogram, illustrating the relationship between depth, depth dose as percentage of air dose and dose rate at a depth. The movable index is located by the point of zero depth and zero per cent depth dose and the intersection of the 100 per cent depth dose and the existing output.

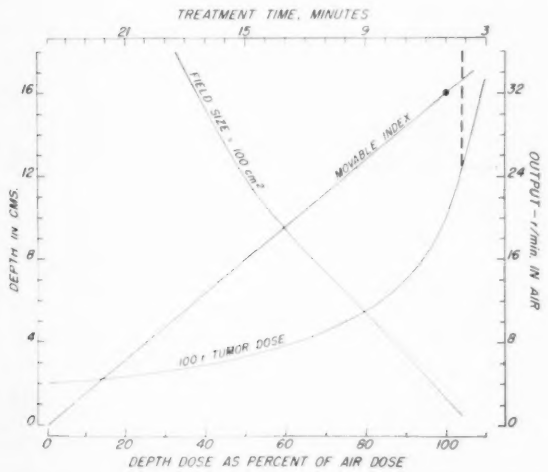

FIG. 2. Telecobalt nomogram for 80 cm. source skin distance. Completion of the nomogram. The prescribed depth dose curves and treatment time scale are related to the depth dose rate scale as shown by the heavily dashed line.

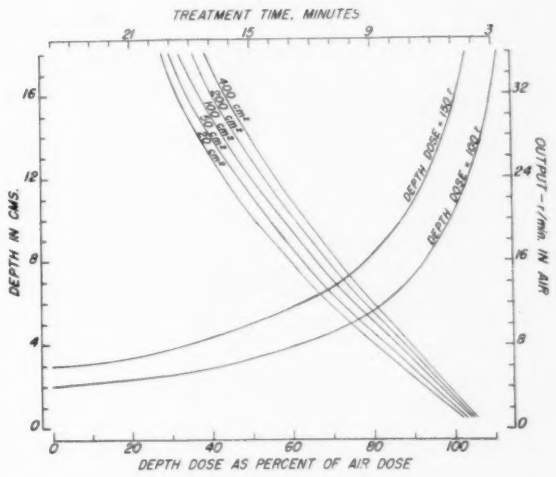

FIG. 3. The complete nomogram less a movable index. The index line may be adjusted to suit individual units.

gram for 80 cm. source skin distance. The movable index has been omitted so that the nomogram may be adapted to other individual units.

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I am indebted to Dr. Charles Botstein, Director of the Radiotherapy Department, for the encouragement he has given me in developing the nomogram and to Mr. R. J. Schulz for his constructive criticism and editorial help in preparing the article.

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FURTHER INVESTIGATION OF THE EFFECT OF ROENTGEN IRRADIATION UPON THE DEVELOPMENT OF THE HEAD OF THE YOUNG AXOLOTL*

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THE previously reported work concerning the influence of local roentgen irradiation on the development of the axolotl head[3,4] has been extended. In this paper are described the areas of the head of young axolotl most sensitive to irradiation and a general picture of the effect of irradiation on the development of the head is given.

MATERIALS AND METHODS

For this investigation, 163 young axolotls (*Siredon mexicanum*) were used. Forty-three animals served as untreated controls, 105 were irradiated with a dose of 3,000 r and 15 with a dose of 6,000 r.

The conditions of irradiation and age of animals at the time of treatment, as shown in Table 1, were almost the same as in the experiments of 1954 and 1955. The very slight differences should have no effect on the results. The animals were anesthetized before irradiation by placing them in an aqueous solution of M.S. 222 (Tricaine methanesulfonate). During irradiation they were arranged in a radial position within a circle on moistened filter paper and their posterior portions were covered with moist cotton. The nonirradiated portions were shielded with a lead covering (made from a 4 mm. lead sheet) having a round radiation localizer about 10 cm. in diameter.[2] After treatment the animals were placed in fresh water where they recovered rapidly from the anesthesia.

Table 1 shows that irradiated and control animals were sacrificed and fixed during a period of three years. Fixations were made using saturated solution of bichloride of mercury with 5 per cent acetic acid and Stieve solution mercuric chloride formalin. Sixty irradiated animals and 10 controls were examined histologically (Table 1) and, in addition, 10 animals from our experiments[3] published earlier were reinvestigated. Therefore, the total number of animals studied histologically over the three year period amounted to 70 experimentals and 10 controls. Percentages of frequency of tissue damage were derived from this number.

The material was embedded in paraffin plus 5 per cent beeswax, and sectioned at 8 or 10 μ. The sections were stained with Ehrlich's hematoxylin and eosin. Photomicrographs were made at different magnifications ($\times$37, $\times$160, $\times$450 and $\times$510). All graphic reconstructions were made by means of camera lucida at a magnification of $\times$37.

GROSS OBSERVATIONS ON THE DEVELOPMENT OF THE TREATED HEAD

Definite growth suppression of the irradiated portion of the head was observed 80–110 days after treatment. This was noted after irradiation with either 3,000 r or 6,000 r. A dose of 3,000 r was lethal in all cases if the complete head was irradiated (all animals died within 6 months after treatment). However, at 3,000 r this dose did not kill all of the animals if only the anterior portion of the head were irradiated, some such animals living more than 20 months. Naturally, in such cases the suppression of growth was especially obvious. The comparison of photographs of animals (Fig. 6, *C-E* and *F-H*) shows how great the suppression of growth was in

* From the Laboratory of Radiobiology, Roswell Park Memorial Institute.
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Table I

CONDITIONS OF IRRADIATION AND NUMBER OF ANIMALS

	1954	1955	1956
Conditions of Irradiation	100 kv., 5 ma., with no external filtration. Intensity, 206 r/min. Target object distance, 18 cm.	100 kv., 30 ma., added filter —5 mm. Al, beryllium window tube; half-value layer 1.25 mm. Al. Intensity 1,390 r/min. Target object distance, 18 cm.	—
Dosage	3,000 r and 6,000 r	3,000 r	—
Number of irradiated animals	40	80	
Number of irradiated animals investigated histologically	20	30 (fixed in 1955)	10 (fixed in 1956)
Age of animals on the day of treatment (days after hatching)	32	25	
Number of control animals	21	22	
Number of control animals investigated histologically	3	5	2
Area irradiated	a) anterior portion of the head b) complete head	a) anterior portion of the head b) complete head	

treated animals. In this case the control animal was younger than the one irradiated, but in spite of this was much larger. The suppression of the rostral end of the irradiated head was especially great. Usually, the growth of the lower jaw was suppressed more than the growth of the upper jaw (Fig. 6, *C*, *D* and *F*).

As a result of the disturbance of development, the visceral arches were exposed (Fig. 6, *C*, *D* and *J*). In normal animals these are always covered. In some animals, asymmetric development of the head was observed a long time after irradiation (Fig. 6*I*). In most animals the eyes had disappeared or rudimentary eyes were covered by skin several months after irradiation (Fig. 6, *E* and *I*).

GENERAL MORPHOLOGIC PICTURE OF THE EFFECT OF IRRADIATION ON THE DEVELOPMENT OF THE HEAD

Graphic reconstructions enabled us to study the general process of development, to coordinate the degree of suppression of various portions of the irradiated head and to compare the development of irradiated animals with the normal development of control animals. The comparison of reconstructions made from sagittal sections of an experimental animal fixed 140 days after irradiation with 3,000 r and 170 days after hatching (Fig. 1) showed the great disturbance in development resulting from irradiation. The most typical was the lack of

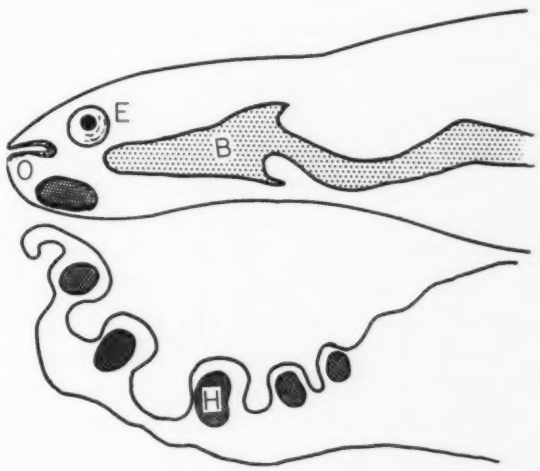

Fig. 1. Partial reconstruction of medial region of the head of animal (II.23) fixed 140 days after irradiation with 3,000 r and 170 days after hatching. Made from sagittal sections. B, brain; E, eye; H, hypobranchiales; O, olfactory chamber.

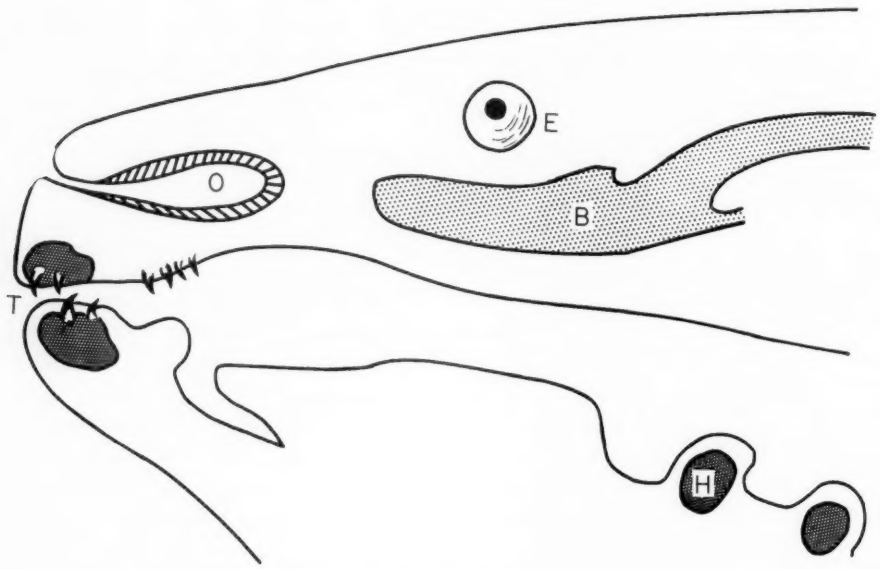

Fig. 2. Partial reconstruction of medial region of the head of control animal (N.85) fixed 206 days after hatching. Made from sagittal sections. B, brain; E, eye; H, hypobranchiales; O, olfactory chamber; T, teeth.

development of the entire anterior portion of the head and the complete disappearance of teeth. The growth of olfactory chambers was suppressed greatly, but these never disappeared completely. In connection with the suppression of the growth of the olfactory chambers, the anterior portion of the brain was also reduced. It was obvious that the growth of the lower jaw was not only suppressed but all of the anterior portion of the jaw had disappeared. As a result of the reduction of the anterior portion of the lower jaw, the visceral (branchial) arches, which give support to the gills, were in an abnormal position. These were shifted in the rostral direction. The magnitude of the shift is shown by comparison with the reconstruction of a control animal (Fig. 2). Normally, visceral arches are situated in the neck region, but in many of the irradiated animals they were located in the anterior portion of the lower jaw.

Figure 3 shows the comparison of reconstructions made from frontal sections of the head of a control animal fixed 98 days after hatching and an experimental animal fixed 90 days after 3,000 r irradiation of the anterior portion of the head and 120 days after hatching. In this case, too, the control animal was younger than the irradiated one but, in spite of this, it was much larger. The olfactory chambers were suppressed in growth and the branchial arches shifted in a rostral direction. The development of the eyes was much more suppressed and they were nonfunctional (the lens and the cornea were absent). The lymphatic nodes, which are very sensitive to roentgen irradiation,[5] were normal in appearance and had a normal size, indicating that the posterior portion of the head was not irradiated. It is noteworthy that the branchial arches, as a result of their shifting, were located in a more rostral position than the lymphatic nodes.

Comparison of the reconstruction of an animal on the day of treatment, 30 days after hatching, with an experimental animal 174 days after a 3,000 r irradiation of the anterior portion of the head, 204 days after hatching (Fig. 4) showed that growth of the irradiated portion of the head was almost completely suppressed and that the anterior portion of the head was almost the same size as on the day of irradiation. The nonirradiated posterior portion of the head of the same animal was greatly enlarged. For example, the size of the lymph nodes

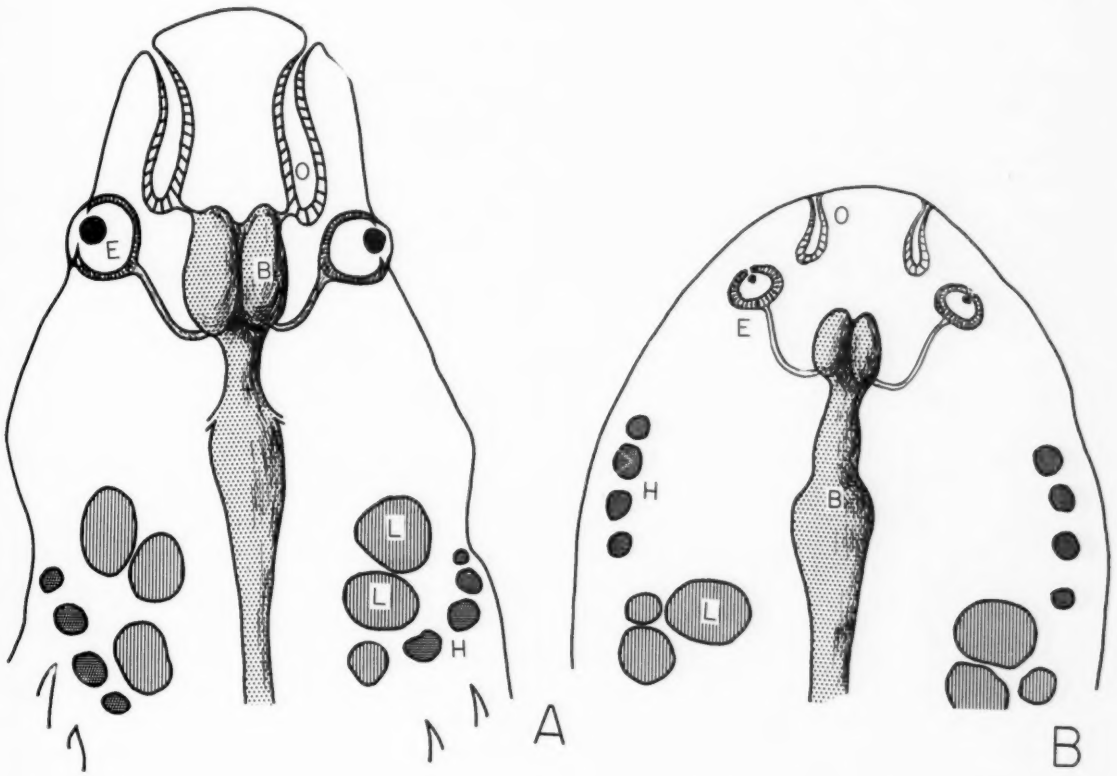

Fig. 3. Partial reconstruction made from frontal sections of the heads. (*A*) Control animal (N.4) fixed 98 days after hatching. (*B*) Animal (VI.105) fixed 90 days after irradiation of anterior portion of the head with 3,000 r and 120 days after hatching. B, brain; E, eye; H, hypobranchiales; L, lymphatic nodes; O, olfactory chambers.

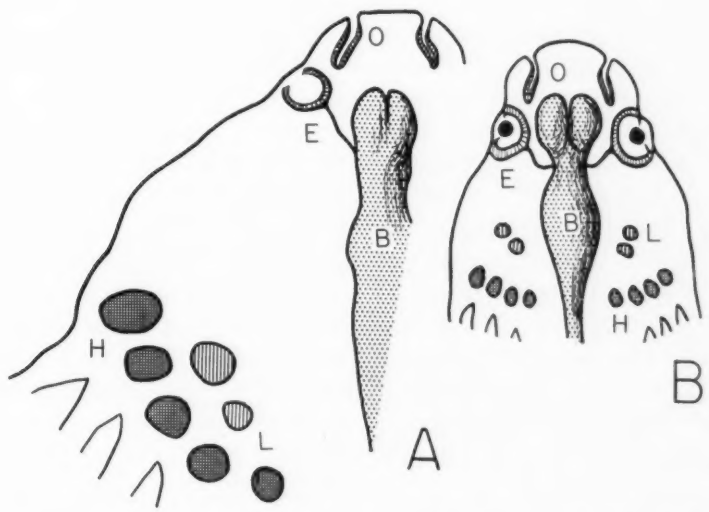

Fig. 4. Partial reconstructions made from frontal sections of the heads. (*A*) Animal (VI.108) fixed 174 days after irradiation of anterior portion of the head with 3,000 r and 204 days after hatching. (*B*) Control animal (N.1) fixed 30 days after hatching. B, brain; E, eye; H, hypobranchiales; L, lymphatic nodes; O, olfactory chambers.

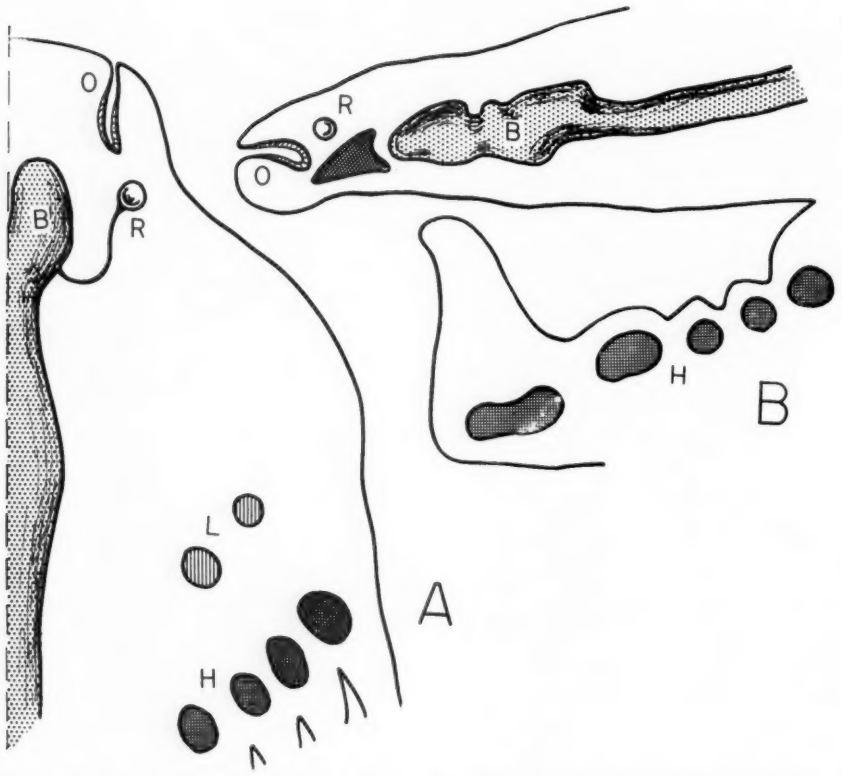

Fig. 5. Partial reconstructions of the head of animal (VI.114) fixed 419 days after irradiation with 3,000 r and 449 days after hatching. (*A*) Reconstruction made from frontal sections. (*B*) Reconstruction of medial region made from sagittal sections. B, brain; H, hypobranchiales; L, lymphatic nodes; O, olfactory chambers; R, rudiment of the eye.

and branchial arches was 3–4 times larger than on the day of treatment.

The last reconstruction of an experimental animal fixed a very long time (419 days) after irradiation of the anterior portion of the head with 3,000 r and 449 days after hatching (Fig. 5) also showed a very great suppression of the anterior portion of the head and especially of the lower jaw. The reduction of the eye was very great in this case. The eye was much smaller than on the day of irradiation (compare Fig. 5*A* and Fig. 4*B*). The lymph nodes were present but much smaller than normal. Possibly this region was partially irradiated in this case (boundary zone of irradiated area).

THE MOST RADIOSENSITIVE AREAS IN THE HEAD

A. *The Teeth.* In the head of the axolotl, the teeth are apparently the most sensitive to roentgen irradiation. According to our data the teeth were completely absent in 88.8 per cent of the animals (Table II). However, teeth were seen in cases where animals were fixed soon after treatment (about 30 days after irradiation), *i.e.*, during the latent period for the disappearance of teeth. With these exceptions we can conclude that teeth were absent in 100 per cent of the animals. According to our previous observations,[8] the resorption of teeth in the irradiated jaws of young axolotls occurred in all irradiated jaws without exception. The teeth disappeared very quickly. Forty-three days after irradiation only very small remnants of teeth were observed, and by the fifty-third day after treatment, all teeth had completely disappeared.

According to Ham[9] the problem of bone resorption is probably a failure in bone maintenance and it is impossible to regard the osteoclasts as specific cellular agents

Table II

COMPARISON OF EFFECTS OF IRRADIATION ON TEETH, LYMPH NODES, OLFACTORY CHAMBERS (FREQUENCY IN PER CENT)

Teeth		Lymph Nodes		Olfactory Chambers	
Absent	88.8%	Absent after irradiation of complete head	100%	Complete replacement of olfactory epithelium by skin epithelium	27.7%
Present	11.2%	Normal after irradiation of anterior head	95%	Abnormal olfactory epithelium without special structures	55.3%
				Olfactory epithelium almost normal in appearance	17.0%

for the resorption of bone. Hence, no special cell is needed to dissolve bone, but special cells are needed to protect it. The same view can be applied for an understanding of tooth resorption. Without activity of cells, which normally supply new substance to the tooth, the tooth anlage begins to dissolve. The complete lack of enamel epithelium is typical of the early picture of damaged tooth anlage. The active role of wandering cells (macrophages) for disappearance of teeth may be important as shown by previous observations. The mechanism of tooth formation and tooth maintenance is permanently destroyed by 2,000 r to 4,000 r doses of roentgen irradiation.

In this study the irradiated jaws contrasted greatly with the normal jaws of control animals (Fig. 6, *K-O*) in respect to normal teeth and formation of new enamel organs. The difference in sensitivity between teeth and eyes was striking and is demonstrated by Figure 6, *O*. In this animal, in spite of the complete disappearance of teeth, the eye was almost normal in appearance.

B. *Lymph Nodes.* In normal axolotls several pairs of large lymph nodes are situated in the dorso-postero-lateral region of the head (boundary region between head and trunk). They are so large and usually stained so densely that it is very simple to find them on the slide even without a microscope. They are always located on the same plane as the eye; therefore, in sagittal and frontal sections, it is possible to find them in the same sections that include the eyes.

According to our previous observations,[5] after total body irradiation with 3,000 r and 6,000 r, the axolotl lymph nodes were seriously damaged in all cases, 75 per cent disappearing completely, while in 25 per cent only small remnants could be found. In the latter cases, the lymph nodes consisted of small accumulations of abnormally large lymphoid cells with large blood vessels between them.

In the present study, as shown in Table II, after irradiation of the complete head, the lymph nodes disappeared in 100 per cent of the cases. After irradiation of the anterior portion of the head, in 95 per cent of the cases the lymph nodes were normal in appearance. In 5 per cent they were slightly abnormal and obviously were partially irradiated because they were in the boundary zone of the irradiated area. This difference can be explained by a slight error in the preparation of the animals for irradiation or by slight movement of the animals during treatment. If animals were placed closer to the center of the irradiated field than was necessary, almost all of the central portion of the head including the region of the lymph nodes would receive some irradiation.

The lymph nodes, as well as other types of lymphoid tissue (peripheral portion of the liver and spleen), are highly sensitive to irradiation.

C. *The Gills.* Damage of the gills during the primary acute reaction[1] is probably important for the evaluation of lethal effect irradiation. Figure 7*A* shows a typical picture of complete degeneration of the gill epithelium of an animal fixed 38 days after irradiation with 3,000 r. The epithelial layer was destroyed and formation of giant

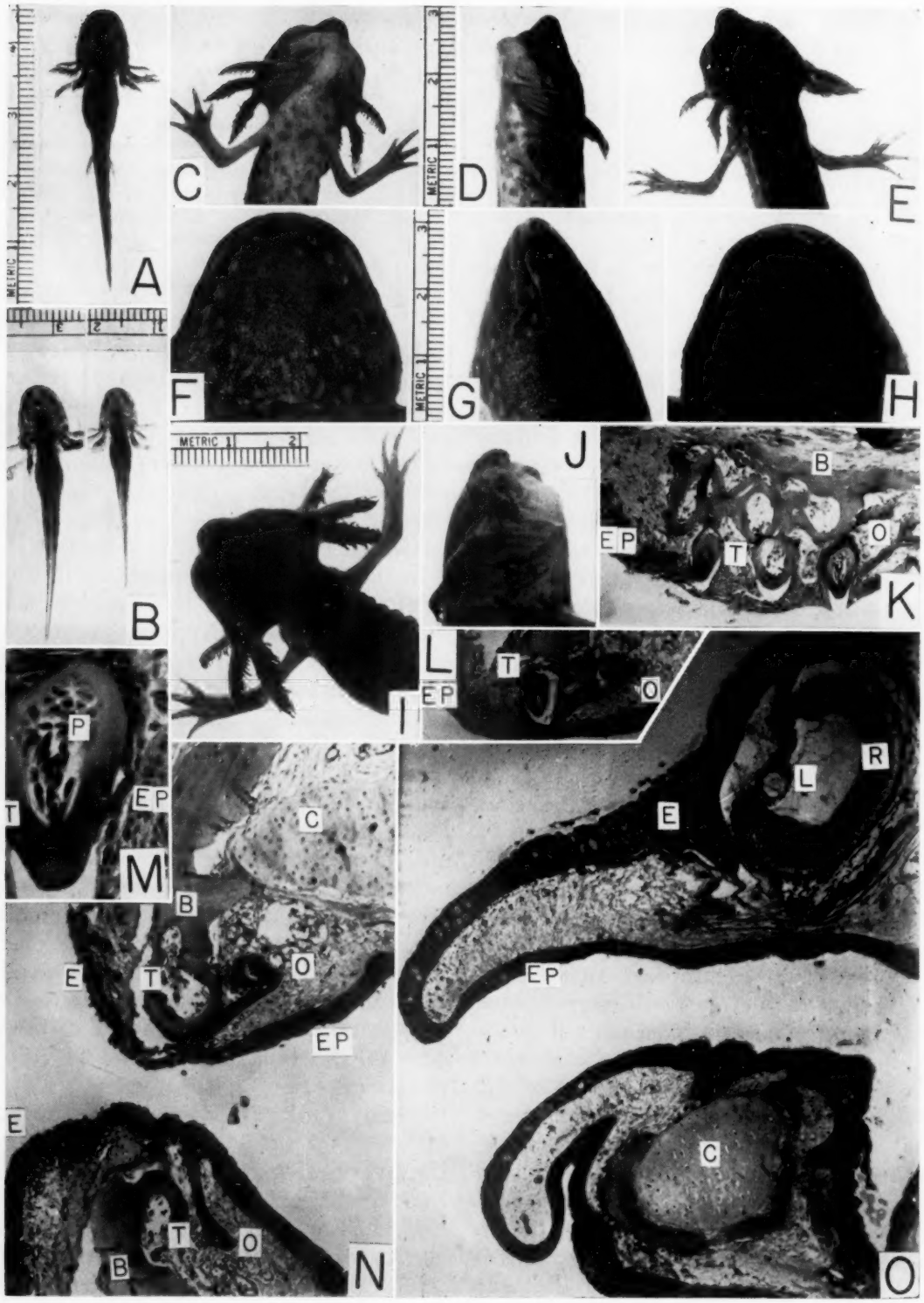

FIG. 6. (*A*) Axolotl 32 days after hatching on day of treatment. (*B*) Axolotls 25 days after hatching on day of treatment. (*C*) Animal (II.25) 213 days after irradiation with 3,000 r of anterior portion of the head and 245 days after hatching. Ventral view. (*D*) The same animal that appears in *C*. Side view. (*E*) The same animal that appears in *C*. Dorsal view. (*F*) Control animal (N.85) 206 days after hatching Ventral view. (*G*)

cells was observed. Comparison with normal epithelium of a control animal (Fig. 7*B*) shows the difference very clearly. Another example is shown in Fig. 7*D* of an animal that was fixed 27 days after irradiation with 6,000 r. The damage was not as great as that shown in 7*A* but still it was obvious. The nuclei of epithelial cells were of giant size (compare with Fig. 7*B*).

For the evaluation of damage to gill epithelium, it is very important to take into consideration the time of fixation. If the gills were fixed during the primary acute reaction (between 20–60 days after treatment), usually we found great damage similar to that described above (formation of giant cells). If the gills were fixed later, the appearance of gill epithelium was nearly normal ("stable state").[1,7] Very often it was possible to see in such epithelium the Leydig cells (Fig. 7*C*), which are very typical for old skin epithelium but not for the epithelium of the gills.

However, in some cases the epithelium of the gills was completely normal shortly after irradiation (between 20 and 60 days). This can be explained by the fact that such gills were not irradiated. It is clear that gills are situated in the boundary region between the head and trunk, and by local irradiation of the head (even if the complete head was included) the gills were not consistently irradiated. This depended on the position of the localizer, movement of animal during the treatment, and state of anesthesia. Therefore, the percentage of damage to the gills is not indicated in Table 11 since such numbers would be meaningless and might even convey the wrong impression. For accurate determination of the sensitivity of gills to irradiation, it would be necessary to make special irradiations of the gill region only.

D. *The Olfactory Chambers.* The reaction of the olfactory chambers to irradiation has not been previously investigated. As mentioned before, growth of olfactory chambers was greatly reduced in all cases, although they never disappeared completely.

The olfactory chambers are large organs that take up considerable space in the anterior portion of the head of the normal axolotl (Fig. 2 and 3*A*). The normal olfactory epithelium has typical structure and forms many sensitive buds, which are modifications of the sensitive cutaneous buds distributed in some regions of the skin. A rich nerve supply is typical. The appearance of the normal olfactory epithelium is in marked contrast with the appearance of the normal skin (Fig. 8, *A*, *C* and *E*). Leydig's cells cannot be found in normal olfactory epithelium.

Normal olfactory epithelium was never found after irradiation. However, in 17 per cent of the cases (Table 11) the epithelium was only slightly damaged. The typical orientation of olfactory cells disappeared. It is necessary to take into consideration that, with one exception, such slightly damaged olfactory epithelium was discovered only after early fixation (between 13 and 36 days postirradiation). From this we can conclude that the olfactory epithe-

The same animal that appears in *F*. Side view. (*H*) The same animal that appears in *F*. Dorsal view. (*I*) Animal (VI.115) 600 days after irradiation with 3,000 r of anterior portion of the head and 625 days after hatching. (*J*) The same animal that appears in *I*. Side view. (*K*) Part of the sagittal section through the upper jaw of the control animal (N.85) fixed 206 days after hatching. B, bone; EP, oral epithelium; O, formation of new enamel organ; T, teeth. Photomicrograph ×37. (*L*) Part of the sagittal section through the upper jaw of the same control animal (N.85) as that in *K*. EP, oral epithelium; O, formation of new enamel organ; T, teeth. Photomicrograph ×37. (*M*) Part of the same section that appears in *K*. T, tooth; P, dental pulp; EP, oral epithelium. Photomicrograph ×160. (*N*) Part of the sagittal section through the jaws of the same control animal (N.85) that appears in *K*. B, bone; C, cartilaginous tissue; E, skin epithelium; EP, oral epithelium; O, formation of new enamel organ; T, tooth. Photomicrograph ×37. (*O*) Part of the sagittal section through the jaws of the animal (VI.102) fixed 48 days after irradiation with 3,000 r and 73 days after hatching. C, cartilaginous tissue; E, skin epithelium; EP, oral epithelium; L, lens of the eye; R, retina of the eye. Photomicrograph ×37.

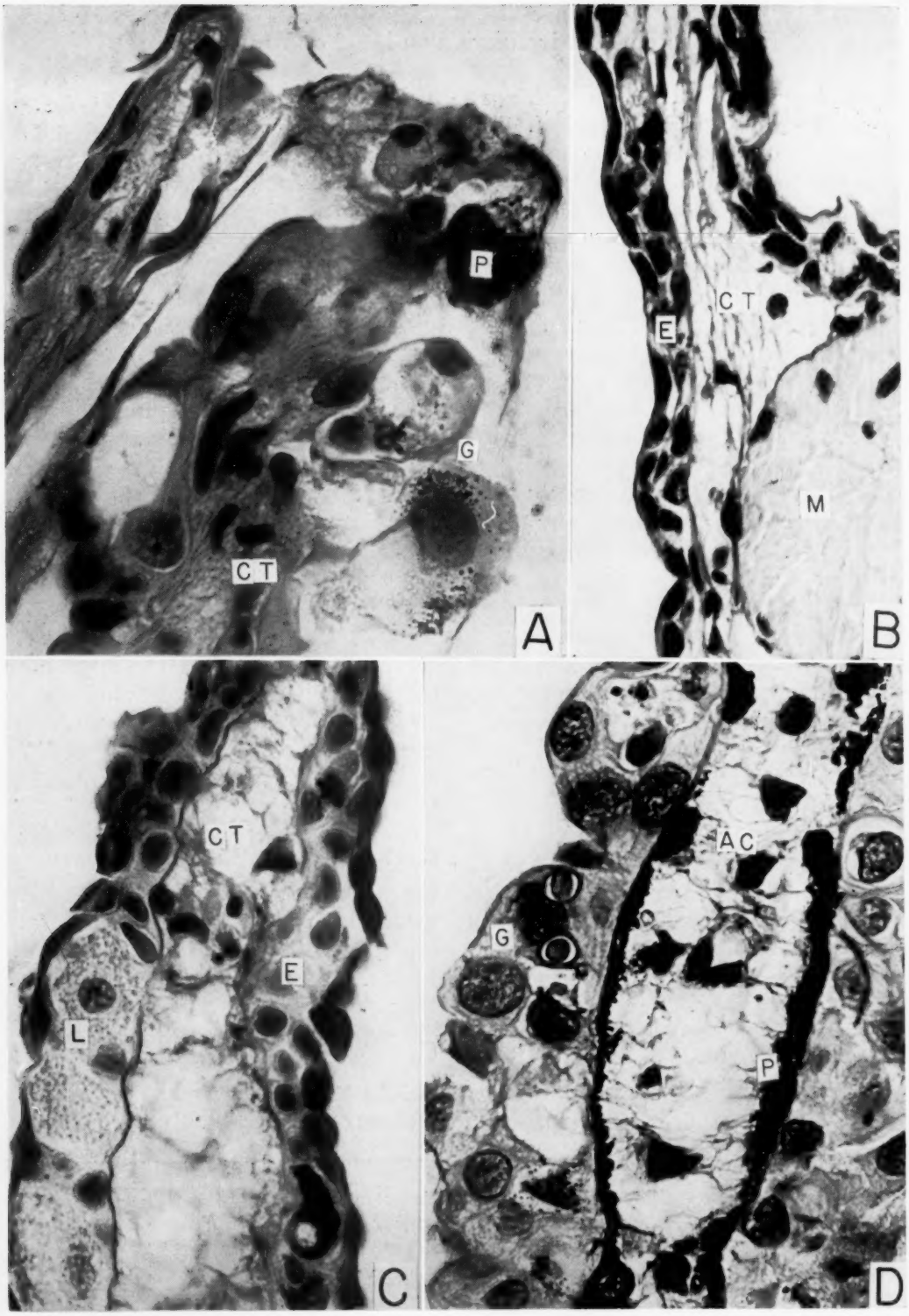

FIG. 7. (*A*) Part of the frontal section through the gill of the animal (LL.14) fixed 38 days after irradiation with 3,000 r and 20 days after hatching. CT, connective tissue cells; G, giant cells; P, pigment cell. Photomicrograph ×450. (*B*) Part of the frontal section through the gill of the control animal (N.52) fixed 89 days after hatching. CT, connective tissue cells; E, normal cells of the epithelium of the gill; M, muscles. Photomicrograph ×450. (*C*) Part of the frontal section through the gill of the animal (II.102) fixed 76 days after irradiation with 6,000 r and 125 days after hatching. CT, connective tissue cells; E, epithelial cells; L, Leydig's cell. Photomicrograph ×450. (*D*) Part of the frontal section through the gill of the animal (II.64) fixed 27 days after irradiation with 6,000 r and 75 days after hatching. AC, abnormal connective tissue cells; G, giant epithelial cells; P, pigment cells. Photomicrograph ×450.

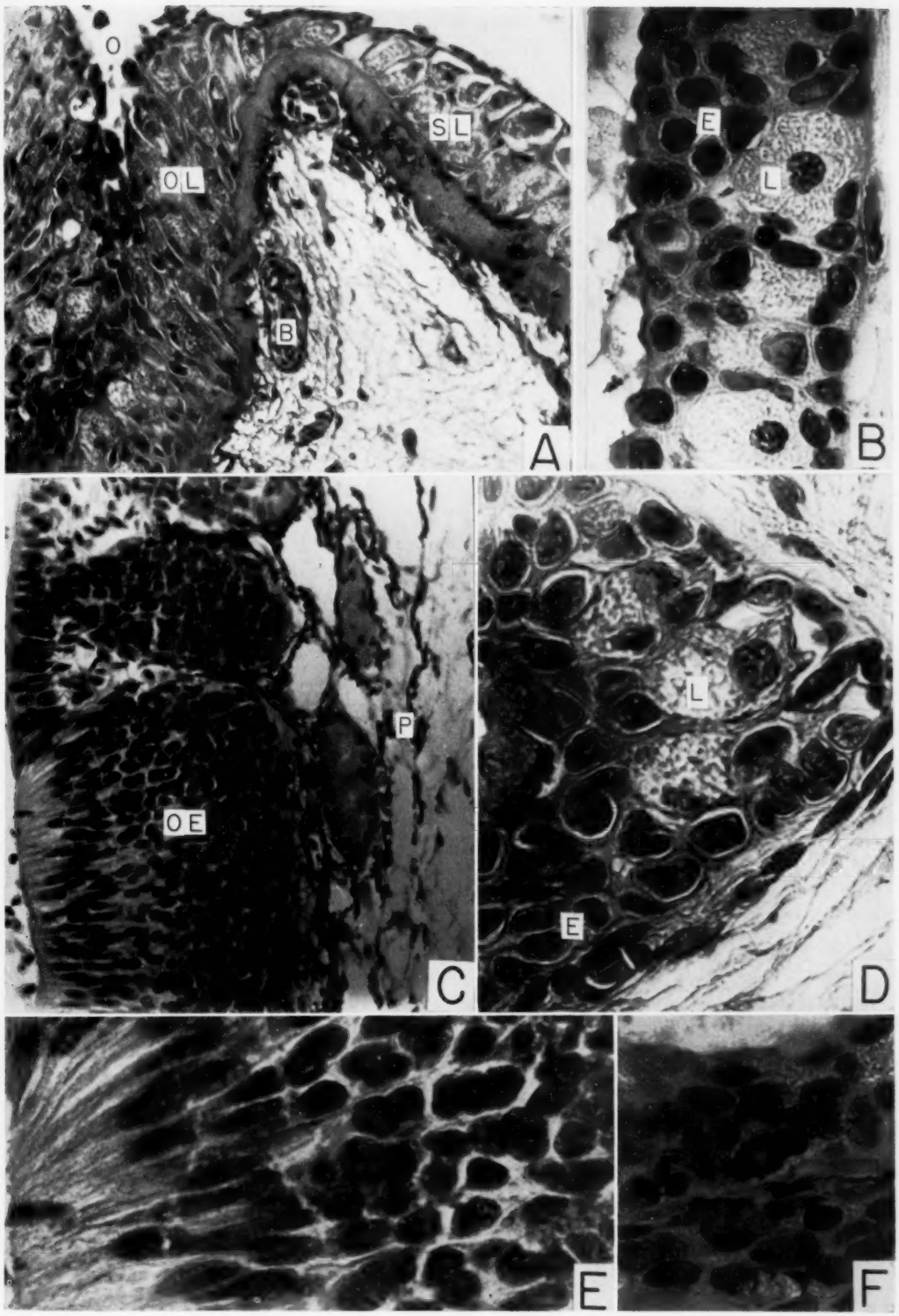

FIG. 8. (*A*) Part of the frontal section through the olfactory chamber of the animal (VI.114) fixed 419 days after irradiation of anterior portion of the head with 3,000 r and 449 days after hatching. B, blood vessel; O, outside opening of olfactory chamber; OL, Leydig's cells in the abnormal epithelium of the olfactory chamber; SL, Leydig's cells of skin epithelium. Photomicrograph ×160. (*B*) Part of the frontal section through the olfactory chamber of the animal (V.88) fixed 173 days after irradiation with 3,000 r of complete head and 198 days after hatching. E, epithelial cells; L, Leydig's cell. Photomicrograph ×510. (*C*) Part of the frontal section through the normal olfactory chamber of control animal (N.85) fixed 206 days after hatching. OE, typical olfactory epithelium; P, pigment cells. Photomicrograph ×160. (*D*) Part of the frontal section through the olfactory chamber of the same animal (VI.114) that appears in *A*. E, epithelial cells; L, Leydig's cell. Photomicrograph ×510. (*E*) Part of the frontal section through the olfactory epithelium of the same control animal that appears in *C*. Photomicrograph ×510. (*F*) Part of the frontal section through the epithelium of olfactory chamber of the animal (VI.108) fixed 174 days after irradiation of anterior portion of the head with 3,000 r and 149 days after hatching. Photomicrograph ×510.

lium reacts with comparative slowness to irradiation. All late fixations gave a clear picture of damage of the olfactory epithelium. In 27.7 per cent (Table II) the olfactory epithelium disappeared completely and was replaced by typical skin epithelium. Figure 8*A* shows such a case in an animal fixed 419 days after a 3,000 r irradiation of the anterior portion of the head. In this animal the olfactory epithelium disappeared completely and no difference between the skin epithelium and the epithelium of the olfactory chamber was observed. The number of Leydig's cells in both cases was the same (compare OL and SL, Fig. 8*A*). Noteworthy is the fact that the Leydig cells in a normal animal are different in various portions of the skin and also vary in different animals. In the animal shown in Figure 8*A*, this number was especially great. Figure 8*D* shows the bottom of the olfactory chamber of the same animal. Epithelium with typical Leydig's cells can be seen. Again, it was possible to see skin epithelium with Leydig's cells in the olfactory chamber of an animal fixed 173 days after 3,000 r (Fig. 8*B*).

In 54.3 per cent of cases (Table II) the olfactory epithelium had not disappeared, but was greatly damaged. We were able to find in such chambers only cells similar to cells of olfactory epithelium (compare Fig. 8, *E* and *F*) but without any special structures of such epithelium. The sensitive olfactory buds disappeared and the distribution of cells in the epithelial layer was completely abnormal. We can conclude that olfactory epithelium is one of the areas of the head most senstive to irradiation.

E. *The Eyes.* In two earlier papers[3,4] major attention was given to the influence of irradiation upon the development of the eye. The considerable data obtained in this study concerning the sensitivity of the lens, cornea and retina to irradiation have already been described.[6]

DISCUSSION

The various tissues and organs of the head of the axolotl may be placed in order of decreasing radiosensitivity into the following five groups: (I) Teeth and lymph nodes, which disappeared completely in 100 per cent of the animals; (II) olfactory epithelium, which disappeared in 27.7 per cent, was damaged in 55.3 per cent and was normal in 17.0 per cent; and lens, which disappeared in 27.7 per cent, was damaged in 55.5 per cent and was normal in 16.8 per cent; (III) epithelium of the cornea, which disappeared in 29.5 per cent, was damaged in 38 per cent and was normal in 32.5 per cent; rods and cones layer of the retina, which disappeared in 30.6 per cent, was damaged in 33.1 per cent and was normal in 36.3 per cent; and gills; (IV) other layers of the retina, which were damaged in 15.5 per cent and were normal in 84.3 per cent; (V) pigment cells of the choroid and other tissues of the head, which were comparatively resistant and did not show any clear signs of damage as a result of irradiation with 3,000–6,000 r, under the described conditions.

The lower jaw was definitely more radiosensitive than the upper jaw and not only was it inhibited in growth, but also reduced in size after irradiation. The cause of this is not clear.

A peculiar damage was generally observed in several organs: The specialized but not completely differentiated tissues can be destroyed by roentgen irradiation, after which they are never restored. Such examples were the oral epithelium that forms enamel organs of the teeth, the olfactory epithelium of the nasal chambers, the epithelium of the cornea, and perhaps the epithelium of the gills. In all these instances the specialized epithelium disappeared completely and was replaced by skin epithelium. A characteristic of this epithelium was the presence of Leydig's cells, that are never observed in differentiated epitheliums of enamel organs, olfactory chambers, cornea or gills. Therefore, it is concluded that specialized but not completely differentiated epithelium is more sensitive to irradiation than the skin epithelium.

SUMMARY

1. The anterior portion or complete head of 120 animals 25–32 days after hatching was irradiated mostly with 3,000 r (in one group of 15 with 6,000 r).

2. Definite suppression of growth of the irradiated portion of the head was observed 80–110 days after treatment. Especially great was the suppression of the rostral end of the head and lower jaw.

3. The study of reconstructions from sagittal and frontal sections showed the following: the teeth disappeared completely; the growth of olfactory chambers was suppressed greatly, but the olfactory chambers never disappeared completely; the growth of the lower jaw was suppressed and its anterior portion had disappeared; as a result of the reduction of the anterior portion of the lower jaw, the visceral arches shifted in rostral direction; the development of the eyes was suppressed.

4. The tissues and organs of the head of the axolotl are placed in order of decreasing radiosensitivity into the following five groups: (I) The teeth and lymph nodes, which were the most radiosensitive; (II) the olfactory epithelium and the lens; (III) the epithelium of the cornea, the rods and cones layer of the retina, and the gills; (IV) other layers of the retina; and (V) the pigment cells of choroid and other tissues of the head, which were comparatively resistant and did not show any clear signs of damage.

5. Specialized but not completely differentiated tissues can be destroyed by roentgen irradiation, after which they are never restored, being replaced by typical skin epithelium with Leydig's cells. This was observed in oral epithelium that forms enamel organs of the teeth, olfactory epithelium of the nasal chambers and epithelium of the cornea.

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Representatives on the American Board of Radiology: Douglas Quick, New York, N. Y.; B. P. Widmann, Philadelphia, Pa.; Frederick W. O'Brien, Boston, Mass.

Representatives on the National Committee on Radiation Protection: Edith H. Quimby, New York, N. Y.; Theodore P. Eberhard, Ann Arbor, Mich.

Representative on the Board of Chancellors of the American College of Radiology: Charles L. Martin, Dallas, Texas.

Forty-second Annual Meeting: The Caribe Hilton, San Juan, Puerto Rico, March 17–19, 1960.

EDITORIALS

LATE REACTIONS FOLLOWING SUPERVOLTAGE RADIATION THERAPY

NEARLY thirty years ago, the term supervoltage was introduced to designate that form of radiation therapy which is carried out with roentgen rays generated at higher voltages than the 200–300 kv. used in conventional deep therapy or, as it is now preferably called following the suggestion of Garland, orthovoltage roentgen therapy. Initially, because of the many technical problems involved, supervoltage radiation therapy was restricted to a few centers. Following World War II, however, due to radical improvements in the design of the electrically operated roentgen-ray apparatus and, more notably, because of the increasing availability of teleisotope apparatus with gamma-ray emissions of similar energies, it has been expanded quite rapidly. At the present time supervoltage radiation therapy is used commonly with roentgen rays of 1–2 mev. and cobalt 60 gamma rays of approximately the same energy. Several cesium 137 units (660 kv.) and an iridium 192 unit (880 kv.) are also in operation.

The physical advantages of supervoltage over orthovoltage roentgen therapy were established through investigations in the early 1930's. Experience since 1951 with the cobalt 60 teletherapy sources has revealed identical advantages. These are: (1) because of the greater depth dose, supervoltage radiation therapy permits the administration of a larger physical dose to a deep-seated tumor; (2) for the same reason, it allows a simplification of technique by reducing the number of portals used for the purpose of cross firing or the number of revolutions in rotational therapy, thus decreasing the volume or extent of the normal structures irradiated; and (3) it permits the deliverance of a given physical dose to a deep-seated lesion with a relatively lesser reaction on the skin. From a practical standpoint this last advantage was considered to be the most important, and is no doubt responsible in a large measure for the rapid recent expansion of supervoltage radiation therapy, especially with teleisotope apparatus.

The question arose from the beginning as to whether these physical advantages can be simply translated into equal biologic effectiveness or whether some relative value (RBE) must be formulated in accounting for the action on the cancer cells and the surrounding normal structures by the two types of radiations. Numerous investigations have been performed in the intervening years to elucidate this problem. Garland[1] in an excellent editorial in this JOURNAL assembled and coordinated the pertinent data published. He arrived at the conclusion that there is a difference in the biologic effectiveness in terms of human cancer cell destruction between orthovoltage and supervoltage rays and that, if the RBE of the orthovoltage rays is unity, the ratio is 0.75. In other words, larger doses must be administered with supervoltage radiation therapy than with orthovoltage roentgen therapy to equate the cancerocidal effect. Garland was careful to state, however, that the ratio mentioned applies only to soft tissue lesions, notably epidermoid carcinoma; and that most of the investigations reviewed involved relatively acute doses and rather short latent periods for evaluation of the results. Therefore, they

[1] Garland, L. H. The relative biological effectiveness of supervoltage radiations. Editorial. AM. J. ROENTGENOL., RAD. THERAPY & NUCLEAR MED., 1957, 78, 902–905.

are not strictly comparable with the aims and results of long term irradiation as practiced in the treatment of human cancer.

Cantril,[2] in the splendid Janeway Lecture delivered before the Thirty-ninth Annual Meeting of the American Radium Society in 1957 in Quebec City, expressed the opinion that the above enumerated advantages of supervoltage radiation therapy are physical rather than biologic attributes. He stated that the RBE of radiations in the higher energy range may be lower by a factor of only 0–10 per cent when compared to orthovoltage roentgen rays and that this differential may or may not apply to all normal as well as neoplastic tissue. His own experiences of some twenty years, utilizing roentgen rays in the range of 800 kv. to 2 mev., led him to the conclusion that any changes introduced by the specificity of supervoltage radiation therapy are of lesser importance than those due to variations in the total irradiated volume, fractionation and protraction of dose. He considers of far greater significance the gradations of radiosensitivity in tumors and within the same tumor and especially the progressive changes in normal tissue. These latter, when the patients were examined many years after irradiation, were not lessened as compared to orthovoltage roentgen therapy; the only difference was that they were observed in the deep as well as in the superficial structures.

An increasing concern about the late changes induced by supervoltage radiation therapy in the normal structures is reflected in several articles published during the last few years. Among the changes discussed are those observed in the supporting connective tissue and in certain organs or systems, as, for example, in the lungs, in the gastrointestinal, urinary and nervous systems, and in some other structures.

The effect of supervoltage irradiation on the subcutaneous connective tissue is easily explained. In orthovoltage roentgen therapy the principal action is on the surface epithelium and the corium with its network of capillary vessels. In supervoltage radiation therapy, the maximum ionization occurs at approximately 0.5 cm. below the skin, at a level containing the elastic connective tissue bundles which extend between the fasciae and the corium. As a result, it is possible to administer considerably larger physical doses to the subcutaneous connective tissue layers, especially when using protracted fractionated techniques, without producing any visible cutaneous erythema, such as is ordinarily observed in orthovoltage roentgen therapy. The late skin reactions following large doses of orthovoltage roentgen rays, whether given singly or in prolonged series, are well known. They consist foremost of telangiectasis and atrophy of the corium, sometimes associated with thickening of the subcutaneous layer. In supervoltage radiation therapy the vascular element may be missing or be relatively slight and fibrosis of the subcutaneous connective tissue layers, fasciae and even the adjacent muscles constitutes the predominating feature. This fibrosis is indolent, being characterized by complete destruction of all tissue cells except the bizarre fibroblast and some enlarged blood vessels. It usually starts with a subcutaneous edema within a few weeks after completion of the irradiation, transforms into a hard induration after approximately three months and becomes a more or less permanent sequela after nine months.

There is accumulating evidence that by using supervoltage radiation therapy a similar type of indolent fibrosis may be developing also in all deep-seated structures where elastic or areolar connective tissue forms the supporting stroma and that this indolent fibrosis may be the causative or, at least, one of the causative factors accounting for the late changes observed in the parenchyma of an organ or in the basic elements of a system. It is an axiom in pathology that fibrosis represents the end

[2] Cantril, S. T. The contributions of biology to radiation therapy. Janeway Lecture, 1957. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., 1957, 78, 751–768.

product of all cellular reactions, whether in a healing process of disease states or in a repair mechanism from manifold injurious actions, including the effects of ionizing radiations.

Among the deep-seated fibrotic reactions, the radiation induced changes within the thorax, particularly the lungs and pleura, lend themselves best to prolonged observation and, in fact, have been amply studied through the years. The first investigations on the histopathologic appearance and time sequence of fibrosis of the lungs and pleura produced by orthovoltage roentgen therapy date back to the early 1920's.[3] It was established at that time that if a certain dose was exceeded, either in a single seance or by fractionation, leukocytic infiltration of the lungs and pleura developed within three to four weeks. In the milder cases, this infiltration usually cleared up within three to six months, leaving minimal scarring of the intrathoracic structures. However, when the dose was considerably larger, the leukocytic infiltration was replaced by fibroblastic proliferation, transforming within approximately nine months most of the lung parenchyma and pleura into dense fibrotic tissue, which then remained permanently. Some of the patients affected with changes of both of these categories have now been studied with periodic roentgenograms of the chest for nearly four decades and thus their clinical significance is well understood.

In using supervoltage radiation therapy over the chest, the chances of similar reactive changes are greatly increased. Rubin, Andrews, Paton and Flick,[4] for example, observed a high incidence of radiation pneumonitis following treatment of esophageal carcinoma with large doses of 2 mev. rotational therapy. Chu, Sved, Escher, Nickson and Phillips,[5] likewise, found that the majority of the cases which received 1 mev. roentgen therapy for pulmonary or mediastinal metastases and several of the cases in which tangential irradiation was used for breast cancer developed radiation pneumonitis. These authors state that the severity of the pneumonitis depended on several factors, among which were the magnitude of the dose, the rate of fractionation and the volume of the lung irradiated, and perhaps others. Several patients died as a result of the radiation pneumonitis, others recovered with minimal roentgenographic changes and others developed persistent pulmonary fibrosis.

The most common radiation-induced reaction of the gastrointestinal tract occurs in the rectum and sigmoid colon during irradiation of the pelvis and less frequently in the esophagus during irradiation of the chest. In both locations it has an acute and chronic phase. The time sequence is similar to that observed in the parenchymatous structures despite the tubular nature of the organs. The acute phase is characterized by a radiomucositis of various degree, while in the chronic phase, there is atrophy and telangiectasis of the mucosa with considerable thickening of the walls of the tube due to surrounding fibrosis. A perusal of the available data in the literature up to 1945[6] on the incidence of factitial reactions following pelvic irradiation in which orthovoltage roentgen therapy was used often in addition to intracavitary or interstitial radium) revealed that late sequelae of the lower gastrointestinal trace were encountered in about 5 per cent of all treated cases, the lowest incidence reported being 3.13 per cent and the highest 16.9 per cent. No data are available on the incidence of the late radiation reactions of the esophagus and it is assumed that with orthovoltage roentgen therapy they occurred rarely.

[3] Evans, W. A., and Leucutia, T. Deep roentgen therapy of neoplastic pulmonary metastases. Am. J. Roentgenol. & Rad. Therapy, 1924, 11, 35–50.

[4] Rubin, P., Andrews, J. R., Paton, R., and Flick, A. Response of radiation pneumonitis to adrenocorticoids. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., 1958, 79, 453–464.

[5] Chu, F. C. H., Sved, D. W., Escher, G. C., Nickson, J. J., and Phillips, R. Management of advanced breast carcinoma. Am. J. Roengenol., Rad. Therapy & Nuclear Med., 1957, 77, 438–447; also Chu, F. C. H., Nickson, J. J., and Uzel, A. R. The effect of ACTH and cortisone on radiation pneumonitis. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., 1956, 75, 530–541.

[6] Leucutia, T. Factitial reactions in connection with irradiation of the pelvis. Editorial. Am. J. Roentgenol. & Rad. Therapy, 1945, 53, 180–183.

Recently, a valuable comparative study on the incidence of the late rectal reactions produced by orthovoltage and supervoltage radiation therapy was published by Fletcher, Brown and Rutledge.[7] These authors arrived at the conclusion that there is a wide margin of dose levels within which an increase in the incidence of late sequelae probably occurs and correlation with other factors is necessary to properly evaluate the findings. However, they also make the interesting statement that in the Radiumhemmet series, where the most important high dose effect comes from radium and is limited to the anterior rectal wall at the level of the posterior fornix, only ulcers limited to that site or rectovaginal fistulae without perirectal fibrosis were observed. At the Holt Radium Institute, on the other hand, where external irradiation plays a greater part and is given in greater amounts, perirectal fibrosis, which Todd called extrinsic reaction, is commonly seen. Similar perirectal fibrosis was observed by Fletcher and his co-workers in their own series, although the incidence has been reduced in the supervoltage group.

Reports on late radiation reactions of the esophagus following supervoltage radiation therapy are sparse, but they indicate a pattern suggestive of the same type of effect as seen in the lower intestinal tract. Smith and Lott,[8] in treating 18 cases of carcinoma of the esophagus with high doses of Co^{60} teletherapy for cure, observed rather severe immediate reactions, followed by mediastinal fistula in 2 cases, pulmonary fibrosis in 1 of 5 surviving cases, which after four years was without symptoms, and esophageal stricture due to fibrosis in another case surviving after thirty-four months.

Late radiation reactions of the urinary tract may be placed in 2 categories: those of the bladder and lower ureters and those of the kidneys. The former occur in connection with irradiation of the pelvis and their pattern conforms with that observed in the rectum and sigmoid colon. The review in 1945[6] indicated that late bladder sequelae following orthovoltage roentgen therapy (often combined with radium) were observed in about 3.5 per cent of the cases. Fletcher *et al.*[7] mention that in the Radiumhemmet series there are relatively more bladder complications than in some others, due to the fact that the plaques are closer to the trigone. In their own series, the bladder complications were the same for orthovoltage and supervoltage radiation therapy.

Possible damage to the kidneys in humans following orthovoltage roentgen therapy was reported as early as 1927 by Doub, Bolliger and Hartman[9] and was fully documented by a long series of subsequent animal experiments by these authors. Chronic diffuse nephritis of the combined interstitial and vascular type followed by steadily progressive fibrous replacement of the parenchyma and sclerosis of the blood vessels was observed in all animals in which the kidneys were directly irradiated. Therefore, avoidance of direct irradiation of the kidneys, especially in young individuals, was recommended. The problem was revived at the Forty-first meeting of the American Radium Society held this year at Hot Springs, Virginia, by Redd[10] who gave an extensive review of the subject and reported the results of comparative animal experiments with 250 kv. roentgen rays and cobalt 60 gamma rays. He also reported a case of nephritis developing after supervoltage irradiation of the abdomen for carcinoma of the ovary.

The possible injurious effect of orthovoltage roentgen therapy on the central nervous system and the enhancement of this effect by supervoltage and especially mega-

[7] Fletcher, G. H., Brown, T. C., and Rutledge, F. N. Clinical significance of rectal and bladder dose measurements in radium therapy of cancer of the uterine cervix. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., 1958, 79, 421–450.

[8] Smith, I. H., and Lott, J. S. Some observations on the effect of cobalt 60 beam therapy on epidermoid carcinoma during the first five-year study period. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., 1958, 79, 406–414.

[9] Doub, H. P., Bolliger, A., and Hartman, F. W. The relative sensitivity of the kidney to irradiation. Radiology, 1927, 8, 142–148.

[10] Redd, B. Radiation nephritis. To be published in the January, 1960, issue of this Journal.

voltage roentgen therapy were already editorially commented upon in this JOURNAL by Krabbenhoft.[11] The damaging effect on the spinal cord of supervoltage roentgen therapy was discussed authoritatively at the Forty-first meeting of the American Radium Society by Dynes and Smedal.[12] These authors observed radiation myelitis during the past nine years in 10 of approximately 800 patients treated with 2 mev. roentgen rays for malignant disease in such a manner that the spinal cord or the medulla was unavoidably exposed to radiation. Two of the 10 patients had the diagnosis confirmed by either biopsy or postmortem examination. Various degrees of hyaline thickening of the vessel walls with swelling of some of the endothelial cells and the appearance of bizarre radiation fibroblasts, accompanied with dissolution of the white matter, were the characteristic findings.

Surprisingly, although it is generally believed that the absorbed bone or cartilage dose is less from supervoltage radiation therapy than from orthovoltage roentgen therapy, Friedman, Southard and Ellett[13] found that the incidence of radionecrosis of bone and cartilage in irradiating lesions of the head and neck is similar to that from orthovoltage roentgen therapy. In their group of 143 cases irradiated with 2 mev. roentgen rays, in two-thirds of which rotation techniques were employed, 10 patients developed radionecrosis of the bone, 3 radiochondritis and 5 radionecrotic ulcer with hemorrhage. They believe that the probable explanation is that anatomic, clinical and pathologic factors contribute much more to the production of radionecrosis than the physical factors.

All in all, it appears that the late reactions following supervoltage radiation therapy constitute a difficult problem, necessitating further exhaustive investigations. Apart from the physical factors involved, the biologic response of the individual tissues must be considered. If one compares the fibroblastic activity produced by orthovoltage and supervoltage radiation therapy in the superficial and deep-seated structures, the difference in the biologic effectiveness does not seem as great as that observed for the cancer cells. Consequently, a dose administered solely on the basis of the estimated equivalent RBE of the cancer cells may prove too high for certain normal tissues, notably the supporting connective tissue, leading to irreversible late sequelae.

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[11] Krabbenhoft, K. L. Radiation injury of the central nervous system. Editorial. AM. J. ROENTGENOL., RAD. THERAPY & NUCLEAR MED., 1955, 73, 850–852

[12] Dynes, J. B., and Smedal, M. I. Radiation myelitis. To be published in the January, 1960, issue of this JOURNAL.

[13] Friedman, M., Southard, M. E., and Ellett, W. Supervoltage (2 mev.) rotation irradiation of carcinoma of the head and neck. AM. J. ROENTGENOL., RAD. THERAPY & NUCLEAR MED., 1959, 81, 402–419.

WILLIAM HARVEY WHITMORE
1892–1959

DR. WILLIAM H. WHITMORE died of coronary heart disease on January 30, 1959. He had been in failing health for several months, and had been retired since August 31, 1958.

Dr. Whitmore was born and spent his early life in Lynchburg, Virginia. He attended the public schools of that city, after which he attended the University of Virginia. He received his M.D. degree in 1916.

After graduation in Medicine, he served approximately six months in the Medical Corps of the Army, as a 1st Lieutenant, after which he transferred to the Navy in January, 1917, in which organization he served during World War I. He was

wounded in action in 1918 while serving with the United States Marine Corps in France and received the Purple Heart. He held many assignments in the Medical Corps of the Navy until his retirement in 1938.

After retiring from the Navy, he entered the private practice of radiology in Norfolk, Virginia, until he was recalled by the Navy and placed on active duty in November, 1940, spending most of the time at the Norfolk Naval Hospital in Portsmouth, Virginia.

After the war he was placed on inactive duty following which he was appointed Radiologist at the DePaul Hospital in Norfolk, where he served until 1951. From then until he retired in 1958, he again entered private practice, and was associated with Dr. P. B. Parsons of Norfolk, Virginia.

Dr. Whitmore was a member of the Norfolk County Medical Society, the Virginia State Medical Society, the American Medical Association, the Virginia Radiological Society, of which he was a past-president, the Radiological Society of North America, the American Roentgen Ray Society, and a Fellow of the American College of Radiology. He made numerous contributions to medical literature.

Dr. Whitmore is survived by his wife, Harriett, two daughters, Mrs. Jane W. Whittemore of Virginia Beach, Virginia, Mrs. Mary Ellen Cheek, of Melbourne, Australia, and one son, William H. Whitmore, Jr., M.D., who is in the practice of medicine in Norfolk, Virginia, and seven grandchildren.

Dr. Whitmore's ability and integrity were recognized by his associates in Radiology as well as his medical colleagues. The high degree of excellence which he exacted from his associates and technical staff was none the less imposed upon himself. His quickness to champion a cause in which he believed, even if unpopular, and his readiness to accept defeat graciously were qualities which were admired by those who knew him.

Clayton W. Eley, M.D.

SOCIETY PROCEEDINGS AND NEWS ITEMS

NEW DIRECTOR AT THE ARMED FORCES INSTITUTE OF PATHOLOGY

Colonel Frank M. Townsend, USAF, MC, has been appointed Director of the Armed Forces Institute of Pathology, Washington, D. C., succeeding Captain William M. Silliphant, MC, USN. Colonel Townsend is the first Air Force Officer to assume the Directorship of the Institute.

Col. Frank M. Townsend

The Armed Forces Institute of Pathology is the central laboratory of pathology for the Department of Defense. In addition to serving the Armed Services, the Institute meets the need of the Public Health Service, The Atomic Energy Commission, Veterans Administration, other federal agencies and civilian pathologists in the form of consultative service.

Colonel Townsend, the senior pathologist of the Air Force, also serves as the consultant in pathology to the Surgeon General, Department of the Air Force.

The American Roentgen Ray Society awards yearly two Fellowships in Radiologic Pathology at the Armed Forces Institute of Pathology.

AMERICAN BOARD OF RADIOLOGY

The spring 1960 examination will be held at the Terrace Hilton Hotel, Cincinnati, Ohio, June 6–10; deadline for filing applications is January 1, 1960. A Special Examination in Nuclear Medicine (for those diplomates in Radiology or Therapeutic Radiology) will be offered provided there are sufficient applications.

NEW RADIUM SOLUTION STANDARDS

The National Bureau of Standards has added a new series of 10^{-9}-g and 10^{-11}-g radium standards to the list of radioactive samples it prepares and distributes. These radium solutions were prepared recently by W. B. Mann, L. L. Stockmann, and A. Schwebel of the Bureau's Radioactivity Section.[1] This new series was made up to restock the nearly depleted and less accurate 1940 supply of radium standards in this range. To provide standards with activities between the 10^{-9}-g and 10^{-11}-g values, new "blank solutions," containing $\sim 0.02 \times 10^{-12}$ g of radium, have also been made available for dilution purposes.

These radium solution standards were issued as part of the Bureau's program to supply standards in all areas of the physical sciences. Radioactivity standard samples, such as these, are especially important, being widely used in the fields of physics, chemistry, biology, and medicine to control processes and maintain accurate equipment and apparatus.

[1] "Preparation of new solution standards of radium," by W. B. Mann, L. L. Stockmann, W. J. Youden, A. Schwebel, P. A. Mullen, and S. B. Garfinkel. *J. Research NBS* 1959, *62*, 21, RP2924.

COURSE IN OPERATIVE RADIUM THERAPY

A course in Operative Radium Therapy is to be offered at the Queens Hospital Center by the Radiation Medicine Department. The course will commence Saturday, October 24, 1959, and will continue for 8 consecutive Saturdays, from 9 A.M.

The program will include the use of interstitial radiation in the oral cavity; radical insertion of radium in the neck; various applicators in carcinoma of the cervix; the Heyman applicators in carcinoma of the endometrium; radium needles in the parametria; and radon, iridium-thread, and cobalt interstitial therapy.

The tuition fee is $100.

Those interested may apply to: Dr. Philip J. Kahan, Supervising Medical Superintendent, Queens Hospital Center, 82-68 164th Street, Jamaica 32, New York.

ORINS CONDUCTS RADIOISOTOPE COURSE IN HEMATOLOGY

The Medical Division of the Oak Ridge Institute of Nuclear Studies will conduct a course in the use of radioisotopes in hematology November 16–20 in Oak Ridge, Tennessee.

This course is designed especially for licensed medical doctors who are interested in hematology and who have some basic knowledge of radioisotopes. The course will emphasize practical details of the use of radioisotopes for diagnostic tests and therapy in blood diseases, and will include information on the hematologic effects of accidental and therapeutic total-body irradiation.

Prospective applicants should write to Mr. William D. Jones, Medical Division, Oak Ridge, Institute of Nuclear Studies, P. O. Box 117, Oak Ridge, Tennessee.

MID-EASTERN CONFERENCE OF X-RAY TECHNICIANS

The Traymore Hotel in Atlantic City, New Jersey, will be the headquarters of the 9th Mid-Eastern Conference of X-ray Technicians sponsored by the Delaware Society, Maryland Society, New Jersey State Society, Pennsylvania Society, Philadelphia Society and the Society of Registered Technicians, Washington, D. C. This conference will convene on November 6, 7, and 8th, 1959, and promises to be a gala affair.

BOOK REVIEWS

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

Lehrbuch der Strahlenheilkunde. Behandlung mit Röntgenstrahlen und radioaktiven Substanzen. By Prof. Dr. med. René du Mesnil de Rochemont, Direktor der Strahlenklinik und -Poliklinik der Universität Marburg. Unter Mitarbeit der Oberärzte der Klinik Dr. H. J. Fiebelkorn, Prof. Dr. Dr. E. H. Graul und Doz. Dr. E. Scherer. Paper. Pp. 763, with 266 illustrations. Ferdinand Enke Verlag, (14a) Stuttgart-W, Hasenbergsteige 3, 1958.

This is an excellent Handbook on Radiotherapy, giving in considerable detail an outline of the technical, physical and biologic basis of radiation therapy, including isotopes. The authors apologize for adding one more to the already available handbooks on this subject. Your reviewer knows of no book in English containing the technical and clinical data on radiation therapy presented in such a thorough fashion as in this book. An English translation should be very popular.

The author realizes that a thorough foundation of physical and biologic relationships involved in radiation therapy is of first importance. Irradiation can and must be applied in many different ways and selection of the method in every individual case must always be based on the personal knowledge and experience of the radiotherapist. The result in each case depends on the individual qualifications of the operator, just as it does in surgery and in many other special fields of medical activity. It was the intent of the author to prepare the reader for appreciation of the treasure of current literary publications.

Radiobiology is a field which has grown to considerable volume. The important basic biologic facts underlying the practice of radiotherapy and radiogenetics, as well as the action of radiation on cells and tissues, have been given special consideration. Some consideration is also given to radiologic chemistry and questions of biologic radiologic protection.

The bibliography seems quite adequate. It will please many English speaking radiologists that generous reference is made to British and American contributions to the literature of radiotherapy.

James T. Case, M.D.

Radioactive Isotopes in Clinical Practice. By Edith H. Quimby, Sc.D., Professor of Radiology (Physics), College of Physicians and Surgeons, Columbia University, New York; Sergei Feitelberg, M.D., Director, Physics Department, The Mount Sinai Hospital, and Associate Clinical Professor of Radiology, College of Physicians and Surgeons, Columbia University, New York; and Solomon Silver, M.D., Attending Physician and Chief, Thyroid Clinic, The Mount Sinai Hospital, and Associate Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University, New York. Cloth. Price, $10.00. Pp. 451, with 97 illustrations. Lea & Febiger, Washington Square, Philadelphia 6, Pa., 1958.

The practice of nuclear medicine is a relatively new field. Most of the literature related to this field has been published in periodicals until recently, when several nuclear medical texts have appeared. Drs. Quimby, Feitelberg and Silver are to be congratulated upon producing a most comprehensive and scholarly text.

The book is divided into three sections, the first dealing with basic physics; the second with instrumentation and laboratory methods; and the third with clinical applications.

Dr. Quimby in the section on basic physics describes the historical aspects of atomic physics and radioactivity and gives a thorough discussion of the background for the average radiologist and physician, with emphasis on those aspects of the field dealing with radioactive isotopes. The part on dosage calculations for radioactive isotopes is particularly noteworthy and deals with the various methods of administration of both beta particle and gamma ray emitting isotopes. The formulas given help to remove to some degree, and to diminish, the inescapable empiricism that attends attempts at dosage estimation in working with these sub-

stances. A special chapter deals with the biologic effects of ionizing radiations and throws into a practical and sensible perspective the fears of late carcinogenesis and the genetic effects of radiation. Detailed consideration of the various aspects of radiation hazards and their avoidance along with a description of methods of disposal of radioactive wastes and removal of contamination concludes this first excellent section of this timely text.

The second section, or Part 2, on instrumentation and laboratory methods by Dr. Feitelberg gives a full description of the various types of radiation detectors used for current isotope techniques. The mathematical and statistical principles involved in application of these techniques as well as the measurements both *in vitro* and *in vivo* situations are discussed. The different types of scanning techniques, autoradiographic procedures and the use of radiation detectors in health survey protection are dealt with *in extenso* and a chapter on laboratory designs is included.

The third section, or Part 3, on clinical applications by Dr. Silver begins with a discussion of thyroid physiology. There has long been a need for an authoritative compilation of the various concepts of thyroid metabolism, many of which have been investigated only through the medium of isotope techniques. The degrees of thyroid behavior in certain disease states as reflected in the various phases of thyroid physiology are lucidly presented. In general, the various tests of thyroid function in the iodide phase, in the phase of transport and in the evaluation of peripheral utilization are well organized and clearly described. A chapter of particular interest is that of pitfalls in the interpretation of diagnostic studies with radioiodine, a field in which Dr. Silver is an acknowledged authority.

The use of radioactive iodine in the treatment of hyperthyroidism, angina pectoris, congestive heart failure, cor pulmonale and such cardiac arrhythmias as superventricular tachycardia, and of thyroid cancer and the methods of altering the response of malignant thyroid tissue are also discussed. A chapter on the treatment of polycythemia, leukemias and malignant lymphomas with radioactive phosphorus and colloidal radioactive gold is practically oriented.

The remainder of this section deals with: the use of Fe^{59} in the study of iron metabolism; the use of Cr^{51} in the study of blood circulation and other fluid compartments of the body; the intracavitary use of radioactive colloids such as Au^{198}, P^{32} and Y^{90} intraperitoneally, intrapericardially and intrapleurally as well as in the bladder; the use of interstitial infiltration of certain types of carcinoma with radioactive colloids, particularly in reference to cervix uteri, prostate and bronchial carcinoma; the use of Sr^{90} and P^{32} in superficial therapeutic applications; and the use of some less common procedures such as the Schilling test, study of the gastrointestinal absorption, performance of hypophysectomy by radioactive isotopes and others.

Convenient conversion factors are presented along with useful physical constants and physical data for isotopes which are commonly employed in medicine.

This book is outstanding in every respect. The authors are to be commended on excellent organization of the material, splendid illustrations and for having very successfully restricted the discussion to those practical clinical applications which have been definitely proved to constitute lasting and solid contributions in the various phases of physiology and treatment.

K. L. Krabbenhoft, M.D.

Atlas of Tumor Pathology. Section XII—Fascicle 40. Transplantable and Transmissible Tumors of Animals. By Harold L. Stewart, M.D., Katharine C. Snell, M.D., Lucia J. Dunham, M.D., and Samuel M. Schlyen, M.D., Laboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland. Paper. Price, $3.50. Pp. 378, with 287 illustrations. Armed Forces Institute of Pathology, under the auspices of the Subcommittee on Oncology, of the Committee on Pathology, of the Division of Medical Sciences, of the National Academy of Sciences—National Research Council, Washington 25, D. C.

With the publication of this volume approximately two-thirds of the fascicles planned for the "Atlas of Tumor Pathology" of the Armed Forces Institute of Pathology have been issued and the generally high standard of its companion fascicles is maintained by this volume.

A comprehensive introduction outlines the history and development of techniques of tumor transmission and transplantation. Particular emphasis is laid on the importance of the genetic relationship between donor and recipient animals, and on the effect of modification of the hormonal milieu of the recipient on

the success or failure of the tumor graft. A total of 50 tumors in various animals are described in detail including their history, pathologic features and techniques of transplantation.

As is customary in these volumes, the text is relatively brief, but it is clearly written and is supplemented by an extensive bibliography. The photographs are superlative. The fascicle makes interesting reading for pathologists and others working in the field of oncology, although its use in the clinical practice of pathology is probably limited. For the experimentalist it will serve as a useful starting reference in the field of tumor transplantation.

A. R. W. Climie, M.D.

BOOKS RECEIVED

The Chemical Prevention of Cardiac Necroses. By Hans Selye, M.D., Ph.D., D.Sc., Professor and Director of the Institute of Experimental Medicine and Surgery, University of Montreal, Canada. Cloth. Pp. 235, with illustrations. The Ronald Press Company, New York, N. Y., 1958.

Vascular Surgery. By Geza de Takats, M.D., M.S., F.A.C.S., Clinical Professor of Surgery, University of Illinois, College of Medicine; Attending Surgeon, Presbyterian-St. Luke's Medical Center and Research and Educational Hospitals, Chicago, Ill. Cloth. Pp. 726, with numerous illustrations. W. B. Saunders Company, Philadelphia and London, 1959.

Personality and Nature in Modern Medicine. By Franz Buchner. Cloth. Pp. 36. Grune & Stratton, Inc., New York and London, 1958.

Symposium über schädliche Wirkungen schwacher Strahlendosen; Physikalische Grundlagen und biologische Aspekte. Federation of Switzerland, The Canton de Vaud, and The Municipality of Lausanne. Paper. Price, $4.25. Pp. 621, with 77 illustrations. Benno Schwabe & Company, Basel, Switzerland. Representative for USA and Canada: Intercontinental Medical Book Corporation, 381 Fourth Avenue, New York, N. Y., 1958.

Atlas of Tumor Pathology. Section VIII—Fascicle 31a. Tumors of the Urinary Bladder. By Nathan B. Friedman, M.D., Director, Division of Laboratories, Cedars of Lebanon Hospital, Los Angeles, California; Clinical Professor of Pathology, University of Southern California School of Medicine; Consultant in Pathology, Los Angeles County General Hospital, and James E. Ash, M.D., Colonel, U.S.A. (Retired), Former Director, Armed Forces Institute of Pathology, Washington, D. C.; Director of Laboratories, Suburban Hospital, Bethesda, Maryland. Paper. Price, $1.00. Pp. 82, with numerous illustrations. Armed Forces Institute of Pathology, under the auspices of the Subcommittee on Oncology of the Committee on Pathology of the Division of Medical Sciences of the National Academy of Sciences—National Research Council, Washington, D. C., 1959. For sale by the American Registry of Pathology, Armed Forces Institute of Pathology, Washington 25, D. C.

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Bronchography. By C. Dijkstra, M.D., Medical Superintendent of "De Klokkenberg" sanatorium and chest hospital, Breda, the Netherlands. Cloth. Price, $9.50. Pp. 157, with numerous illustrations. Charles C Thomas, Publisher, Springfield, Ill., 1959.

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Acta Radiologica Supplementum 174. Slipping Epiphysis of the Hip; A Roentgenological and

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Acta Radiologica Supplementum 175. Studies on the Distribution and Fate of C^{14}- and T-Labelled P-Aminosalicylic Acid (PAS) in the Body. By Åke Hanngren. Paper. Price, Sw. Kr. 25:–. Pp. 118, with 53 illustrations. Acta Radiologica, Box 2052, Stockholm 2, Sweden, 1959.

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The Mast Cells. By James F. Riley, M.B., Ch.B. (Hons.), M.D., Ph.D., D.M.R.T., F.R.C.S.E., Consultant Radiotherapist, Royal Infirmary, Dundee, Lecturer in Radiotherapy, University of St. Andrews. Cloth. Price, $6.75. Pp. 182, with 65 illustrations. E. & S. Livingstone, Ltd., Edinburgh; and Williams & Wilkins Co., Mount Royal and Guilford Aves., Baltimore, Maryland, 1959.

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The Collected Statistics of Malignant Disease Seen at University College Hospital, London During the Period 1946–1950. Compiled by the Cancer Follow-up Department, University College Hospital, London. Cloth. Pp. 632. Wilding & Son Ltd., Castle St., Shrewbury, England, 1958.

ABSTRACTS OF RADIOLOGICAL LITERATURE

Department Editor: T. Leucutia, M.D., Harper Hospital, Detroit 1, Michigan

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RADIATION THERAPY

Massoud, G. E., and Awwad, H. K. Scleroma of the upper air-passages; a clinico-radiological study of 84 cases. *J. Fac. Radiologists*, Jan., 1959, *10*, 44–49. (From: The Radiological Department, University of Alexandria, Alexandria, Egypt.)

Scleroma is a specific granuloma usually affecting the nose, but the pharynx, larynx and bronchi may also be involved. The histologic picture is characteristic. The corium and submucosa are infiltrated by granulomatous tissue composed of vacuolated foamy histiocytes, degenerated hyalinized plasma, plasma cells, neutrophils, capillaries and fibrocytes, fibroblasts and collagen. The causative agent is a strain of the Friedländer bacillus. The mode of infection is uncertain but seems to come from the soil. It is endemic in Easter Europe, Russia and South America. It is also endemic in Egypt.

This granuloma starts as a submucosal infiltration and thickening in the nose, sinuses and nasopharynx. The first lesion is red, soft and nonulcerated and forms polypoid masses. Ulceration, crusting and discharge occur later. Fibrosis develops eventually and the granuloma becomes pale, firm and pitted. New active granulomatous infiltrations can occur in the scarred areas.

Roentgen signs are thickening of mucosa, either diffuse or polypoid; expansion of the nasal cavity with thinning and erosion of the nasal bones; in some instances, there is thickening and sclerosis of the nasal bones; there may be depression of the floor of the antrum and the soft palate may be increased in size.

Antibiotics clear up secondary infection, but the most effective treatment is radiation therapy. Obviously, the richly cellular lesions with abundant blood vessels respond better than those with fibrotic changes. Three different dose levels are used: 600–1,000 r in two to four weeks is considered a small dose; the medium dose, which is most effective, is 1,500–2,000 r in three to four weeks; and the high dose is 3,000–4,000 r in five weeks. The high dose, of course, leaves permanent skin changes.

If the case responds to radiation therapy and remains asymptomatic for one year, the chance for recurrence is slight. The laryngeal lesions are more intractable than the nasal lesions. These were treated with moderate dosage.

Where this disease is endemic, it must be differentiated from tumors, tuberculosis and syphilis, and any widening of the nasal cavity with thinning of nasal bony boundaries and septum is roentgenologically suggestive of scleroma.

Very excellent roentgenographic reproductions illustrate the various phases, there are also photographs of lesions in the nose and mouth. Three tables of data are included.—*Eva S. Carey, M.D.*

Ironside, William M. S., Carpender, James W. J., Roedal, Robert, and Lindsay, John R. Carcinoma of the larynx; results obtained by surgery and external radiation in ninety-three cases. *J.A.M.A.*, Feb. 21, 1959, *169*, 783–786. (Address: W. M. S. Ironside, 950 E. 59th St., Chicago 37, Ill.)

Ninety-three cases of laryngeal carcinoma, treated prior to 1953, were reviewed in this series.

Classification was made in accordance with the recommendations of the International Committee (ICPR, Copenhagen, July, 1953) into lesions of the (1) supraglottic area, including the ventricle, ventricular folds, and infrahyoid portion of the epiglottis (27 cases—10 survivors); (2) glottis-vocal cords (65 cases—43 survivors); and (3) subglottis (1 case—1 survivor).

Clinical stages were: Stage I, carcinoma limited to mucosal membrane; Stage II, carcinoma infiltrating, but limited to the larynx; Stage III, carcinoma extending beyond the larynx, movable lymph nodes; Stage IV, skin involvement, or fixed lymph nodes, or distant metastases.

The results obtained by surgery and external radiation therapy are compared (supervoltage was not used in this series).

Surgical treatment consisted of biopsy excision (1 case), laryngofissure, laryngectomy, and radical neck dissection of metastatic lymph nodes together with laryngectomy.

Radiation therapy was given through opposed lateral portals with localization of the lesions by pointers, plaster jackets and roentgenograms. The technical factors employed were as follows: 200–250 kv., half-value layer of 1.5 mm. Cu to 3 mm. Cu, target skin distance of 50 to 80 cm. Most patients received a tumor dose of 5,000 to 5,500 r in thirty-five to forty-two days, resulting in a wet dermatitis over the treated skin. During treatment, the patients were observed by radiotherapists and otolaryngologists and follow-ups were made at frequent intervals.

From their results, the authors conclude that in the supraglottic group, primary surgery is preferable to either irradiation or combined therapy. This should include bilateral neck dissection. They recommend this approach since supraglottic lesions have a high incidence of cervical metastases, often clinically undetectable, in which external irradiation has little effect. An over-all five year survival of 37 per cent was obtained in supraglottic carcinoma comprised of Stage II and Stage III cases.

In the glottic Stage I lesions, little difference in the results was observed between surgery and irradiation —in this series amounting to an 80 per cent five year survival. Primary irradiation has the advantage in Stage I lesions of preserving voice and allowing the possibility for future surgery before the disease progresses beyond the Stage I or Stage II.

In glottic Stage II lesions, the early cases—in which cord movement was diminished but not fixed—received radiation therapy; those with fixed cords were subjected to primary surgery (laryngectomy). This method of subjecting early Stage II cases to irradiation first and reserving operation avoids laryngectomy in some and preserves the larynx for years in others until it is necessary. This requires meticulous follow-up observations in order to detect any recurrence early.

In glottic late Stage II, Stage III, and Stage IV lesions and where evidence of subglottic or supraglottic extension is present, surgery including bilateral neck dissection should be used.—*Bernard S. Loitman, M.D.*

Liegner, Leonard M., Olson, Marshall, and Nickson, James J. Postoperative irradiation of 86 cases of carcinoma of the cervix. *Surg., Gynec. & Obst.*, March, 1959, *108*, 313–320. (From: Department of Radiation Therapy, Memorial Center for Cancer and Allied Diseases, New York, N. Y.)

Brunschwig and Daniel reported that if carcinoma remained following pelvic exenteration no survivals resulted. In their series of 36 patients where disease remained and no radiation therapy was given, the average survival was three months. One patient survived for sixteen months.

This article was written as an attempt to answer the question of the value of postoperative irradiation. Eighty-six patients, from 1948 to 1956, whose primary treatment for carcinoma of the cervix was surgery, were studied. They were referred for postoperative roentgen therapy by the gynecology service at Memorial Hospital. There were four postoperative categories defined:

1. The completely excised group, 15 cases. No gross or histologic evidence of tumor remaining at surgery.

2. Postoperative recurrent cancer group, 27 cases. Same criteria as in Group 1 but with recurrence in the follow-up period.

3. Postoperative persistent cancer group, 24 cases: (A) proved persistence by histologic examination, 11 cases; (B) surgeon's opinion or histologic evidence of cancer near excisional margins, 13 cases.

4. The explored group: nonresectable or distant lymph node involvement, 20 cases.

By using the League of Nations classification, the distribution was as follows: Stage 0, 13; Stage I, 24; Stage II, 33; Stage III, 10; and Stage IV, 6.

The majority of the patients received million volt therapy employing opposing pelvic or abdominal (inverted T) fields. The port size was usually 200–400 cm.^{2} with 3,000–5,000 r tumor dose delivered in twenty-one to forty-two days.

A total of 6 patients, or 6.9 per cent, survived five years. There were 2 patients in Group 1, 2 in Group 2, 2 in Group 3B and none in Group 4. Survival beyond eighteen months was considered good palliation. Twenty-nine patients did survive more than eighteen months but only 8 of these had disease proved clinically or by biopsy at the onset of roentgen therapy.

Of the total group, 58 had disease, proved clinically or by biopsy at the time therapy was instituted (20 explored, 11 proved persistent, and 27 postoperative recurrent). Two of these 58 survived five years (3.4 per cent) and 8 survived more than eighteen months (14 per cent). This is considerably better than the average of three months survival, with a maximum of sixteen months, with no postoperative irradiation as reported by Brunschwig and Daniel.

It is interesting to note that of the cases with positive lymph nodes, 32 patients had involvement of the common iliac or para-aortic lymph nodes as compared with 12 patients who had involvement of the obturator or hypogastric lymph nodes at surgery. This would seem to reinforce the belief that the pelvic ports used in the nonsurgical (radium and roentgen) treatment of carcinoma of the cervix should be lengthened.—*Paul M. Inlow, M.D.*

Newton, K. A., Humble, J. G., Wilson, C. W., Pegg, D. E., and Skinner, M. E. G. Total thoracic supervoltage irradiation followed by the intravenous infusion of stored autogenous marrow. *Brit. M. J.*, Feb. 28, 1959, *1*, 531–535. (From: Westminster Hospital, London, England.)

One of the deterrents in the use of large volume high dosage radiation therapy in treatment of metastatic disease has been the inevitable and often permanent damage to the bone marrow element with resulting hypoplasia. Stored autogenous marrow has been used previously to combat this hematopoietic depression which follows large volume radiation therapy. The body's ability to accept it has been demonstrated by several investigators.

In this study, 2 patients with advanced metastatic pulmonary disease (osteogenic sarcoma and Ewing's sarcoma) were administered total thoracic 2 mev. irradiation with 3,000 r tissue dose in two weeks.

Stored autogenous marrow was given. In case I, marrow regeneration became evident in thirteen days. The patient continued her hematopoietic improvement over the next two months. She died in her third month with signs of progressive dyspnea, cyanosis and weakness. No postmortem examination was obtained.

In case II, regeneration of marrow was demonstrated one month following the marrow infusion and at the time of writing, two months later, the patient was doing well. Chest roentgenograms have remained clear of recurrent disease.—*Bernard S. Loitman M.D.*

Notter, G., and Helander, C. G. Über den Wert der Cavographie bei Diagnose und Behandlung retroperitonealer Testistumormetastasen. (The value of cavography in diagnosis and treatment of retroperitoneal metastases of testicular tumors.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Oct., 1958, *89*, 409–417. (From: Allgemeine Abteilung des Radiumhemmet, and Röntgendiagnostische Abteilung des Karolinska Krankenhauses, Stockholm, Sweden.)

Cavography was performed by direct, bilateral, percutaneous injection of the femoral vein 2–3 cm. underneath the inguinal ligament and introduction of a catheter 5 cm. upward. Seven to ten cc. of 30 per cent urografin per second was injected. One set of roentgenograms was taken in flat supine position, the other set after new injection with 45 degrees of obliquity to the right. The examination was performed only in ambulatory patients. Out of 33 cavographies on 28 patients, 13 were in carcinoma and 20 in seminoma cases. In seminomas 14 of the patients had negative cavography, and in carcinomas 5 had negative results. The basic change in cavograms consisted of indentation or displacement of the vena cava, especially at the level of L-1 to L-4.

The authors draw the following conclusions: (1) Definite positive cavography is proof of metastatic lesions. (2) Negative cavography does not encompass definite metastases if (a) they are very small or (b) if they are located in the region of the iliac vessels, in the bifurcation of the aorta, or in the perirenal area on the left side. The latter locations can be additionally cleared by pyelography or renography. (3) Also, in cases lacking epigastric metastatic symptoms, cavography most of the time is negative. (4) The 14 positive cavographies were 12 cases in consensus with clinical symptoms or operative findings, respectively.

The indication for cavography could be based on the following practical rules: (1) Cavography is not necessary in new seminoma cases without clinical signs of epigastric metastasis. (2) Cavography is of great help in suspect recurrence of seminomas for the objective demonstration of metastases. (3) In carcinomas positive cavography is extremely important as an indication for surgical lymphadenectomy. On the other hand, massive changes in cavograms contraindicate surgery, since the condition is inoperable.

In addition to cavography, pelvic phlebography, urography, and renal venography may be necessary. In therapeutic cases cavography is a useful method for demonstration of regression of metastatic lesions. —*Nathan Kriss, M.D.*

Klapproth, Hans J. Wilms tumor: A report of 45 cases and an analysis of 1,351 cases reported in the world literature from 1940 to 1958. *J. Urol.*, May, 1959, *81*, 633–648. (From: The Division of Research of the Cleveland Clinic Foundation, and The Frank E. Bunts Education Institute, Cleveland, Ohio.)

This paper is a report of 45 cases of Wilms's tumor in children and adults treated at the Cleveland Clinic from 1921 to 1958, and an analysis of 1,351 cases collected from the world literature from 1940 to 1958.

Wilms's tumor accounts for approximately 20 per cent of all malignant tumors in childhood. In spite of all attempts at earlier diagnosis and prompt treatment by various methods, the end results indicate a poor prognosis in this disease.

Wilms's tumor may arise in any portion of the kidney and may vary greatly in size and extent. This tumor is often nodulated, is gray or of flesh color, and is encapsulated in a rather dense fibrous capsule. A cross-section may disclose hemorrhagic cysts, necrotic cavities, fat, cartilage, bone, fibrous tissue and blood vessels. Invasion of the renal vein has been frequently observed and, in this series of cases, is reported in 45 per cent of patients. Metastases occurred to the lungs, liver, bones and contralateral kidney; less frequently to the skin, brain and urinary bladder.

Wilms's tumors may be associated with other congenital anomalies in the urinary tract. Reports of bilateral Wilms's tumors are difficult to evaluate because they may be either metastatic or primarily bilateral. Likewise it is frequently impossible to properly assess reports of the congenital origin of Wilms's tumor.

In the series of cases under review, the author includes 22 patients in whom Wilms's tumor occurred in the fetus, newborn or stillborn infant. Twenty-two tumors occurred in infants a few weeks old and were assumed to be present at birth.

Although the incidence of Wilms's tumor in the adult is low, it does occur as late as the eighth decade of life. The author has added 2 new cases to those previously reported, bringing the total number of cases in adults to 108.

There is no evidence that Wilms's tumor is a familial disease, although 8 familial cases have been reported in a total of 2,000 patients with this disease.

The symptoms are usually negligible until an abdominal mass is noted by the parent or patient. Fever and abdominal pain and hematuria are late symptoms. Anorexia, nausea and vomiting, loss of weight, and cachexia occur in the final stages of the disease. Hypertension has been observed in some patients, presumably on the basis of perirenal inflammatory reaction, constriction of blood vessels or thrombosis. In some patients hypertension was reversed by nephrectomy, in others there was only a temporary reversal.

A palpable tumor mass in the abdomen of a child

is sufficient indication for immediate suspicion of either a Wilms's tumor or a neuroblastoma.

In patients with Wilms's tumor intravenous urography usually reveals a large renal parenchymal shadow with distortion of the pelvis and calyces. In some instances, where renal function is severely disturbed, retrograde pyelography may be necessary, but the diagnosis can usually be established by intravenous urography. Needle biopsy is not recommended as a diagnostic procedure.

The experience of the author indicates that the methods of treatment which produce the best end results are: (1) nephrectomy followed by postoperative irradiation; (2) preoperative irradiation, nephrectomy and postoperative irradiation; (3) preoperative irradiation and nephrectomy. Some authors have reported a cure rate as high as 47 per cent, but the over-all cure rate for the large series of patients included in this article is 20–27 per cent. Nephrectomy alone gave 20.9 per cent cures, preoperative irradiation and nephrectomy 27.1 per cent, nephrectomy and postoperative irradiation 26.2 per cent, and preoperative irradiation nephrectomy and postoperative irradiation 24.1 per cent of a total of 1,351 patients.

The value of radiation therapy is well established; however, the poor final results indicate need for earlier diagnosis. In this respect it is interesting to note that patients treated prior to the age of one year have a better prognosis than those of the older age group. Radiation therapy should be employed in every case operated on for cure, because it will improve the end results. Those patients who survive the first postoperative year have a good prognosis, since 85 per cent of those who succumbed did so during the first year. The prognosis for those having survived two years is good and those surviving and being without metastases or local recurrence after three years can be considered as cured.—*George W. Chamberlin, M.D.*

Kiefer, Everett D., and Smedal, Magnus I. Radiation therapy for stoma ulcer occurring after subtotal gastrectomy. *J.A.M.A.*, Jan. 31, 1959, *169*, 447–451. (From: Departments of Gastroenterology and Radiology, The Lahey Clinic, Boston, Mass.)

Stomal ulcer occurring after operation is a serious complication which usually presents a much more difficult therapeutic problem than the primary duodenal ulcer. In patients who were subjected to resection of a stomal ulcer, a second stomal ulcer developed in 14.5 per cent. Cases have been reported in which ulcers recurred after all but a tiny remnant of stomach had been removed. The problem here is how to eliminate the persistence of free HCl in the secretions of the gastric stump. Most clinicians will agree that total gastrectomy is too radical a surgical procedure for a benign condition. The idea of using irradiation in a deliberate attempt to produce gastritis, and thereby reduce gastric secretion, in cases of duodenal ulcer was first suggested by Bassler (1909). During the last ten years, several studies have been made on the value of gastric irradiation in the treatment of peptic ulcer.

Peptic ulcers occurring opposite the stoma after Billroth II operations were studied in 23 patients. In order to reduce the secretion of acid by the gastric remnant, irradiation was used. The tissue dose was approximately 1,800 r in all cases. The resulting reduction in gastric acidity was variable and unpredictable. Achlorhydria or pronounced hypochlorhydria was achieved in more than half of the patients up to two years after irradiation. Because suppression of gastric secretion is not always complete or permanent, follow-up studies should be carried out for recurrent ulcer or acid secretion. Further treatment should be instituted if either condition is found. Radiation doses from 1,600 to 1,800 r can be repeated one or two times at intervals of six months without serious danger or untoward side effects. There is evidence that, if achlorhydria persists for three years after treatment, no further ulceration is to be expected.

The results obtained in this small group of patients give some hopeful indication that the recovery of acid-secreting power of the fundal stump is not as likely to occur as it is in the case of the irradiated intact stomach and that, if achlorhydria or nearly complete achlorhydria is once established, it may persist.—*J. T. Ling, M.D.*

Hummon, Irvin F., Magalotti, Marion F., and Grigg, Emanuel R. N. A case of follicular lymphoma. *Radiology*, Feb., 1959, *72*, 227–233. (Address: I. F. Hummon, Department of Radiology, Cook County Hospital, Chicago 12, Ill.)

The group of diseases designated as malignant lymphoma manifest themselves in a wide variety of ways as to the rapidity and extent of involvement of organs, and in the survival time after the onset of the first symptoms. Although the outcome is invariably fatal, there are cases in which the clinical course is markedly protracted. This is especially true in the so-called giant follicular or Brill-Symmers type lymphoma. The authors present one such case in which the disease had been controlled for eleven years after the onset of symptoms. Treatment consisted only of external roentgen therapy. A total of 38 different ports were irradiated according to the site of occurrence in a period of five years (1950–1955). Of the 38 ports, 25 were located in the extremities. Total dosage to various areas was as low as 250 r (air) and as high as 2,866 r (air). A table and diagram are presented to outline the areas treated and the dosages used. At the time of writing, more than three years had elaspsed since the last roentgen

treatment in May, 1955, and the patient has remained asymptomatic and clinically free of lymphoma. At no time was there any evidence of visceral (liver, spleen, bowel, etc.) involvement. Despite the large number of ports used and the large cumulative radiation dose absorbed, there was no evidence of damage to the blood-forming organs. The authors feel that external irradiation is the treatment of choice for this disease, and, if judiciously used, will give good symptomatic relief and increase survival time in these patients.

A brief discussion of the pertinent literature is presented.—*Z. Petrany, M.D.*

Schäfer, Heinrich. Extragenitales Chorionepitheliom bei einem Mann. (Extragenital chorionepithelioma in a male.) *Strahlentherapie*, Feb., 1959, *108*, 283–287. (From: Röntgen-Radium-Klinik der Städt. Krankenanstalten, Aachen, Germany.)

A thirty-six year old man developed chest symptoms, gynecomastia, and general evidence of systemic illness; he finally died of cerebral metastases. A clinical diagnosis of extragenital chorionepithelioma was based on demonstration of an anterior mediastinal tumor with pulmonary metastases, gynecomastia, and normal genitalia.

External radiation therapy was directed to the chest in combination with cytostatic therapy (mitomen) and the chest symptoms and findings regressed. At autopsy the thoracic tumors consisted solely of necrotic tissue without recognizable chorionepithelioma, in contrast to the cerebral and other non-irradiated tumors which showed hemorrhagic chorionepitheliomatous tissue.—*Henry G. Moehring, M.D.*

Elekema, H. Harrison, Scanlon, Paul W., Colby, Malcolm Y., Jr., and Ulrich, John A. Thrush complicating radiotherapy of the mouth and neck. *Radiology*, Jan., 1959, *72*, 26–29. (From: The Mayo Foundation, and the Sections of Therapeutic Radiology and Bacteriology of the Mayo Clinic, Rochester, Minn.)

Intensive radiation therapy to, or adjacent to, the mouth frequently produces a gray-white membranous lesion superimposed on a radiomucositis. In the past this membrane formation has been assumed to be a direct effect of radiant energy.

The authors report 7 patients who developed such membranous lesions of the mouth while receiving either roentgen or cobalt 60 therapy for local malignant disease. In all 7 cases cultures of the membrane were positive for *C. albicans*, and in the 4 cases in which direct examination of the smears was performed, the organism was found growing in the filamentous form in the membrane.

The authors feel that the observed pathologic overgrowth of *C. albicans* is due, in part, to radiation damage to tissue, plus alteration of the normal mouth flora caused by changes in the secretions of the salivary glands. Recognition of oral moniliasis is important, since the usual oral antiseptics are ineffective. Nystatin is recommended as the best drug available at present.—*Edward B. Best, M.D.*

Ng, Elmer, Chambers, Frank W., Jr., Ogden Harry S., Coggs, Granville C., and Crane, Jackson T. Osteomyelitis of the mandible following irradiation; an experimental study. *Radiology*, Jan., 1959, *72*, 68–74. (Address: E. Ng, 1111 University Drive, Menlo Park, Calif.)

Osteomyelitis of the mandible is a common complication following irradiation of cancers, the fields for which include the mandible. It has been stated that preliminary tooth extraction reduces the incidence of this complication. Quick and Paterson, however, recommend postponement of the extraction. More recently, Wildermuth and Cantril have proposed that extraction of teeth prior to irradiation actually predisposes to osteomyelitis. In the present study, two groups of adult mongrel dogs received between 3,000 r and 8,000 r to both the right and left side of their mandibles. One group had had extraction of the teeth on the right side approximately sixteen days prior to the beginning of irradiation. The treatment schedule and technique were identical throughout for both groups: 250 kv., 50 cm. target-skin distance, 5×5 cm. port, 1.4 mm. Cu half-value layer, 105–110 r (air) on alternate days for a total of fifteen days.

The experimental results and conclusions are as follows: (1) Removal of teeth prior to irradiation significantly decreased the incidence of osteomyelitis (only 3 of 14 edentulous hemimandibles developed osteomyelitis as compared with 12 of 14 in the dentulous group); (2) gingival ulceration and osteomyelitis of the mandible occurred following exposure to irradiation of 4,000 r (air) or more, under the conditions of this experiment; (3) osteomyelitis was not observed in the absence of gingival ulceration; and (4) bone necrosis did not occur in the absence of osteomyelitis with the dosage and time range studied.

Photographs of the gross and pathologic specimens are presented to show the various stages of post-irradiation change in the mucosa, teeth, and mandible.

The sequence of events in the development of osteomyelitis based on pathologic findings was as follows: (1) Ulceration of the gingiva; (2) extension of the inflammation into the peridontal membrane and through the lamina dura to involve the medullary cavity of the mandible and the apices of the teeth; and (3) further destruction of the peridontal membrane with exfoliation of teeth.—*Z. Petrany, M.D.*

Lanier, Raymond R., and Wikle, Walter T. The clinical significance of "SR" (sensitization response to radiation) in normal vaginal mucosa. *Radiology*, Feb., 1959, *72*, 217–221. (From: University of Colorado Medical Center, 4200 East Ninth Avenue, Denver 20, Colo.)

Some women, while receiving radiation therapy for carcinoma of the cervix, have certain distinctive changes in the Papanicolaou smears of epithelium desquamated from an otherwise normal vagina. These changes which consist of an increase in cell size, nuclear degeneration, and vacuolization and abnormal staining of the cytoplasm were described by Graham and Graham, who named the phenomenon "radiation response" or "RR." These investigators believe that the percentage of "RR" cells correlates with the patient's chance for five-year survival after treatment with roentgen rays and radium. The Grahams later reported a correlation between the five-year survival rate of cervical carcinoma following radiation therapy and the changes in the appearance of the vaginal "basal" cells on Papanicolaou smears performed before irradiation. These cells appeared as though they had been irradiated, but had not, and the phenomenon was termed "sensitization response" or "SR" since it seemed to predict the efficacy of radiation therapy. If these reported "RR" and "SR" changes are valid and reliable they could be of immense clinical value in the differential selection of cervical cancer patients for postirradiation surgery.

To further evaluate these reported "SR" changes, the authors studied a group of 96 patients with cervical cancer in whom pretreatment Papanicolaou smears were available for study. All patients have been treated since 1950 by radiation therapy at the University of Colorado Medical Center. The authors report that, in their series, there is no "SR" correlation with either the time of survival, the stage of the disease, or the age of the patient. Likewise there is no significant "SR" difference in the living and the dead. The authors agree with the Grahams that these cytologic changes are real and not artefacts, but that their significance remains undetermined.—*Edward B. Best, M.D.*

Lamarque, P., Pourquier, H., and Leenhardt, P. Analyse des possibilités techniques dans la télécobalthérapie des tumeurs du sein. (Analysis of the technical possibilities of telecobalt therapy in tumors of the breast.) *J. de radiol., d'électrol. et de méd. nucléaire*, Jan.-Feb., 1959, *40*, 15–23. (From: Centre anticancéreux de Montpellier, Montpellier, France.)

The authors report their experience with telecobalt therapy over a two year period in the treatment of breast tumors. The immediate advantages of this method are especially noteworthy when applied to the internal mammary, axillary, retro- and supraclavicular areas. Specifically, it is possible to treat the lymphatic chains of these areas without encountering the serious skin reactions seen with conventional roentgen therapy. Various isodose curves are presented.

As far as direct irradiation of the breast is concerned, which is necessary in certain cases, it is preferable, according to the authors, to employ conventional roentgen therapy, reserving telecobalt therapy for the more intensive treatment by permitting a complementary dose of irradiation without aggravating the skin reactions.—*Maurice Dufresne, M.D.*

Sahler, Otto D. Development of a room specifically designed for total-body irradiation. *Radiology*, Feb., 1959, *72*, 266–267. (Address: Mary Imogene Bassett Hospital, Cooperstown, N. Y.)

The work of Barnes and his associates on the treatment of mouse leukemia with roentgen rays and homologous bone marrow has suggested a possible new approach to the treatment of human leukemia. In the event that this technique is translatable to man two conditions will be necessary: first, a source of transplantable bone marrow; second, a source of near-uniform total-body irradiation.

To prepare for such an eventuality the author obtained consultation with Massachusetts Institute of Technology, General Electric Company and Picker X Ray Corporation regarding total-body irradiation. This group concluded that optimum distribution could be achieved by two sources of radiation at an angle of 180° to each other and that cobalt 60 would be the best source. On the basis of these recommendations the author designed a room for such therapy wherein one source is a 1,000 rhm unit, which can be used for more conventional therapy, and the other source is a 750 rhm industrial unit mounted on rails. The room is designed so that a distance of 3 meters from each source can be obtained, although most total-body treatments will be at a distance of 2 meters.—*Edward B. Best, M.D.*

RADIOISOTOPES

Williams, S. F. Symposium on a medical reactor installed at the National Naval Medical Center. *Radiology*, Dec., 1958, *71*, 851. (From: U. S. Naval Hospital, Bethesda 14, Md.)

The physical factors of a 5-watt medical reactor, which was installed as an integral part of the isotope branch of the Radiology Service of the United States Naval Hospital, Bethesda, Maryland, are presented. The reactor is a unit fabricated with three concentrically located waterproof metal tanks. The inner core

tank contains the fuel, a stock of uranium-impregnated disks of polyethylene. It is bisected by the "glory hole," a 1 inch diameter tube for irradiation of samples. The bottom disks of fuel are pierced for the insertion of fuel-tipped rods by which various power changes are obtained. A thermal-sensitive fuse holds the upper- and lower-half fuel disks together. A dangerous increase in temperature will melt the fuse and cause the disks to fall, separating the core and preventing uncontrolled increase in neutron flux. The larger tank, known as the reactor tank, containing the reflector and the gamma shield completely surrounds the core tank. The graphite reflector, in which neutrons interact with carbon atoms, causes some neutrons to return to the core. Four access ducts, accessible from outside the biologic shield, pass through the reactor tank and are available for sample irradiation. The reactor is designed to operate within a narrow range of temperature variation, approximately 13° C. Flux-measuring BF^3 counters and boron-lined ion chamber neutron detectors are located inside the water-filled outer shell tank.

This medical reactor is the first such installation for use by a hospital department for medical purposes only.—*Arno W. Sommer, M.D.*

Shea, Thomas E., and Sharp, Robert. Physical factors of a low-power medical reactor. *Radiology*, Dec., 1958, *71*, 852–855. (From: National Naval Medical Center, Bethesda, Md.)

It is anticipated that, within a few years, all fighting ships will be propelled by nuclear power. This conversion brings with it a need for increased knowledge of protection problems and more experience in the field of neutron exposure. It therefore seemed desirable that there be available at the National Medical Center a neutron source from which further data might be obtained. A small medical reactor could act as a training unit. It would also provide a neutron source for study of the effects of neutrons on man and animals. Primarily, however, it would be a source of short half-life isotopes, which could be utilized in clinical medicine.

The medical reactor which was installed at the National Naval Center is the first reactor operated by a hospital department for medical purposes only. The reactor is described in detail in subsequent papers.—*Arno W. Sommer, M.D.*

Druyan, Robert, Mitchell, T. G., King, E. R., and Spencer, R. P. Neutron activation analysis. *Radiology*, Dec., 1958, *71*, 856–859. (From: U. S. Naval Hospital, Bethesda 14, Md.)

Neutron activation analysis is a twofold procedure; first, radioactivity in a specimen is induced by exposure to a neutron flux, and then the induced radioactivity is analyzed by the application of counting procedures to the radioactive emissions. The amount of produced radioactivity may be calculated according to a known formula; likewise, by algebraic manipulation of this equation, the weight of the unknown element can be calculated on an absolute basis, assuming the activity is known. However, in practice it is more practical to irradiate a weighed standard at the same time and determine the weight of the unknown on the basis of relative activity of the standard and unknown samples counted in sequence under the same conditions. Using this technique, material suitable for such determinations is limited because of the failure to produce countable quantities of radioisotopes from certain elements, or because of the excessive time required for 95 per cent saturation (5 half-lives); nevertheless, the range of material suitable for such determinations is wide, and in most instances quite sensitive.

Activation of a biologic specimen results in the production of a variety of radioisotopes of markedly differing concentrations and activities, and masking of the emissions is the natural consequence which causes analysis to be far more difficult. Using this technique, in the case of gamma-counting procedures, sodium is probably the one biologic element which is amenable to direct and simple analysis. In specimens of extracellular material, sodium can be directly analyzed without further preparation after several hours to allow for the decay of other ions. Analysis for other ions in the presence of sodium necessitates relatively complete isolation, if analysis by gamma counting is to be performed. Sodium must be removed in most situations, especially with extracellular fluid specimens, and, depending upon the element sought, its concentration, and ability to sustain activation an appropriate fraction, free from other radioactive ions, must be isolated. This may be accomplished by simple decay for longer half-lived isotopes. However, the determination of certain elements requires isolation into appropriate fractions, preferably prior to activation, because of their very short half-lives. The technique of ion-exchange columns has been used to remove sodium from solution. Beta counting techniques have also been used in conjunction with neutron activation. The use of differential absorption may prove valuable in distinguishing between beta emissions of sufficiently different strength and thus allow direct analysis without the necessity of ion separation.—*Walter H. Jarvis, Jr., M.D.*

King, E. R., Maxfield, William S., Sharp, Robert, and Druyan, Robert. The production and medical applications of short-half life radioisotopes. *Radiology*, Dec., 1958, *71*, 860–867. (From: U. S. Naval Hospital, Bethesda 14, Md.)

The activity of any radioisotope that can be produced by the neutron gamma reaction depends upon

several factors, *i.e.*, flux neutron capture cross section, number of target atoms introduced, and irradiation time. By the application of certain formulae, one can determine the maximum weight in grams that can be irradiated and still allow enough reactivity to produce a self-sustained chain reaction, and the total radioactivity it is possible to produce for various target materials and irradiation times. Thus, there are many factors that determine the production of radionuclides in a low-power reactor, and these must all be considered in evaluation of a reactor for medical application. After production, the greatest problem is that of separation of the radioisotope from the stable materials to obtain sufficient specific activity, particularly to eliminate any danger of toxicity when certain elements are administered, and to remove contaminants. The Szilard-Chalmers process, chromatography, and ion exchange procedures have been used in this connection.

The use of short-half-life radioisotopes will decrease the tissue radiation dose delivered to the patient and allow repeated studies to be performed at relatively brief intervals. The following clinical applications of the short half-life isotopes are being investigated: a thirty-minute radioiodine uptake using I^{128} as a "screening" test to eliminate euthyroid patients from further studies with I^{131} and to allow repeat studies on the same patient at brief intervals (three or four hours) in order to test the effects of many drugs and environmental conditions upon thyroid function; the use of Cu^{64} in positron scintiscanning for brain tumor localization and study of size and location of liver lesions; the use of Cu^{61} and Mn^{56} for blood-volume studies; the use of Cl^{38} in dilution and space studies and in the determination of serum chlorides, and the use of radioisotopes to determine the amount of other electrolytes in the blood, urine and tissues.—*Walter J. Jarvis, Jr., M.D.*

Chambers, F. W., Jr., and Duckworth, J. W. The AGN-201-M reactor thermal column. *Radiology*, Dec., 1958, *71*, 868–870. (From: Naval Medical Research Institute, Bethesda 14, Md.)

A AGN-201-M 5-watt reactor located at the National Naval Medical Center in Bethesda, Maryland, is a potentially valuable tool for biologic research. The thermal column is a large tank 34 inches in diameter and 24 inches deep. Flux measurements made in this tank, with and without a 4 inch lead shield, when it contained either water or graphite, have shown a useful neutron flux available at the top of the column. Therefore, it seems that investigation of the biologic effects produced by extended exposure to low neutron dose levels would appear feasible. The large cross-sectional area of the column might accommodate test animals up to the size of small swine.

The extent, however, to which this reactor can be used for biologic experiments is not known at present. Many studies must be made to determine how the ratios of the several types of radiations might be changed, what the spectral distribution of the various radiations would be under these circumstances, and what effect the presence of these various systems plus biologic specimens of different sizes in the thermal column might have on the reactivity of the reactor.—*Donald N. Dysart, M.D.*

Blomfield, G. W., Eckert, H., Fisher, Monica, Miller, H., Munro, D. S., and Wilson, G. M. Treatment of thyrotoxicosis with ^{131}I; a review of 500 cases. *Brit. M. J.*, Jan. 10, 1959, *1*, 63–74. (From: Department of Pharmacology and Therapeutics, University of Sheffield, and Sheffield National Centre for Radiotherapy, Sheffield, England.)

Results of treatment of thyrotoxicosis with I^{131} in a group of 500 patients are reviewed in some detail in a careful study featuring extended follow-up evaluation. In general, the results agree with those of other large series, with 70 per cent of cases brought to euthyroidism by a single dose. The authors found no difference in their ability to control hyperthyroidism, whether accompanied by diffuse or nodular enlargement of the gland. Recurrences and complications were identical in these two groups.

Post-treatment hypothyroidism was encountered in 12 per cent of all patients treated. The authors found this complication arising most often in those patients who had been treated for clinical hyperthyroidism in the absence of palpable abnormality of the thyroid gland. It also was not uncommon in a group of patients treated for postoperative recurrence of hyperthyroidism. In both of these instances it is possible that the authors exceeded their usual dosage scale because of their inability to estimate the volume of a rather small amount of thyroid tissue.

The authors raise an interesting point by describing hypothyroidism occurring late after treatment, with 8 patients becoming hypothyroid at from eighteen to more than forty-eight months after one or more doses of I^{131}.

Also of interest is the report of a detailed study of the distribution of I^{131} in the body of a patient who died within four days of the administration of 13.5 mc of I^{131}. Tissue doses were calculated on the basis of the distribution figures, and some of the results follow: Thyroid gland, 8,300 rads; testis, 103 rads; blood, 42 rads; a number of other tissues, 16 to 44 rads. It should be noted that the testis dose calculated from this study is more than twice that of blood or any of the other tissues assayed. No reason for this specifically high dose is advanced. The results should be borne in mind, and added to other human distribution data as they appear in the literature.—*Frederick J. Bonte, M.D.*

Sheline, Glenn E., Lindsay, Stuart, and Bell, H. Glenn. Occurrence of thyroid nodules in children following therapy with radioiodine for hyperthyroidism. *J. Clin. Endocrinol. & Metabol.*, Jan., 1959, *19*, 127–137. (From: Departments of Radiology, Pathology and Surgery, University of California School of Medicine, San Francisco, Calif.)

I^{131} was used to treat 213 cases of toxic diffuse goiter from 1945 to 1953. Five of the cases were less than ten years of age when treated and 2 of these developed nodules eight and ten years later, respectively. One case out of 13 treated between the ages of ten and twenty years developed nodules five and one-half years after therapy. Nodules were found in only 2 of the 195 adult cases twelve and fifteen months later, respectively, after treatment. No further cases of nodules were observed in the adults at a later time.

The case reports of the 3 children who developed nodules are presented in detail.

Case I was a five and one-half year old girl who was treated with 2 mc of I^{131}. The thyroid activity remained at the upper range of normal. Ten years later the thyroid gland was approximately one and one-half times normal size and contained nodules. Subtotal thyroidectomy showed 2 nodules which were classified as follicular adenomas.

Case II was a nine year old girl who was treated with 1.2 mc of I^{131} and sixteen months later was given 0.5 mc of I^{131}. Four years later she was given an additional 3.7 mc of I^{131} for a recurrent thyrotoxicosis and a nodule in the right lobe of the thyroid gland. The nodule disappeared. Eight years later, 3 nodules were found at the time of subtotal thyroidectomy and 2 of the nodules were classified as follicular adenomas. The third was an invasive adenoma or a low grade follicular carcinoma.

Case III was a seventeen year old girl who was given 3.6 mc of I^{131} and five years later a lump was noticed in the thyroid gland and subtotal resection showed a 3.5 cm. nodule which was classified as a follicular adenoma.

It is believed that the nodules in the children represent true neoplasms. Studies upon rats whose thyroid glands have been irradiated with I^{131} show that the benign and malignant neoplasms that appeared in the thyroid glands originated as foci of nodular hyperplasia and regeneration. It is believed that carcinomas may develop in previously benign adenomas.

This study showed that nodular hyperplasia of the thyroid gland may occur if functional thyroid tissue is left in young patients treated with I^{131} for diffuse toxic goiter. The authors believe that it would be safer to produce hypothyroidism and give replacement therapy in those cases under the age of twenty years that require treatment with I^{131} for diffuse toxic goiter.—*Charles W. Cooley, M.D.*

Lum, Carl H., Marshall, William J., Kozoll, Donald D., and Meyer, Karl A. The use of radioactive (I^{131}-labeled) rose bengal in the study of human liver disease: Its correlation with liver function tests. *Ann. Surg.*, March, 1959, *149*, 353–367. (From: The Cook County Hospital, Cook County Graduate School of Medicine, and the Northwestern University Medical School, Chicago, Ill.)

The authors studied 231 patients with radioactive rose bengal (potassium salt of tetraiodotetrachlorofluorescein) to determine the value of the test in correlating liver and blood levels and to compare it with standard liver function tests.

The patients were grouped as follows: Normal hospital controls—48 patients; cirrhosis of the liver—71 patients; infectious hepatitis—53 patients; calculous obstruction—23 patients; carcinoma obstructing the extrahepatic bile ducts—36 patients.

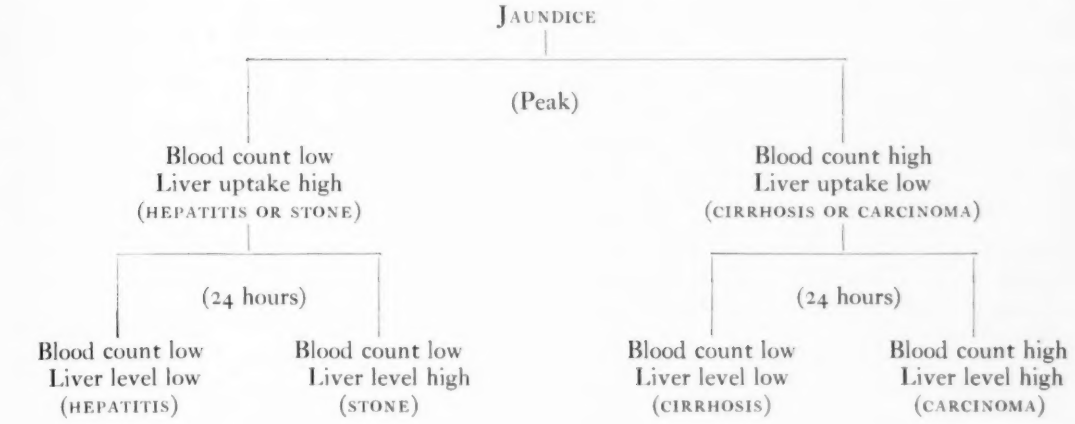
Icteric index, alkaline phosphatase, total protein, albumin globulin ratio, thymol turbidity and gamma globulin turbidity determinations were obtained on all patients the day of examination.

A standard dose of 5 μc of radioactive (I^{131}) rose bengal solution was injected intravenously. Gamma ray activity was measured over the liver using a scintillation counter and an Esterline-Angus recorder until maximum uptake was obtained in the liver (thirty to ninety minutes). At this time a 1 cc. blood sample was obtained and measured in a well counter. Recordings and blood samples were repeated at six and twenty-four hours.

The normal patients showed the highest levels over the liver and the lowest blood levels. The lowest liver levels were obtained in those patients with cirrhosis and carcinoma, while the patients with hepatitis and calculus showed intermediate levels. Uptake rates were obtained by dividing peak levels by the time in minutes, and excretion rates were found by dividing the time into the difference between the peak and the six and twenty-four hour liver levels.

The radioactivity over the liver, the uptake and excretion rates and the blood levels were separately grouped and statistically analyzed. The liver uptake rate and the blood levels were then correlated with the liver function tests and statistical analyses were made. All of the results are illustrated by numerous tables, graphs and scattergrams.

A theoretic scheme for using this test in the differential diagnosis of jaundice is proposed, by determining both liver uptake and blood levels during the first forty-five to ninety minutes and at twenty-four hours. The early liver and blood levels result in two significant combinations, while the twenty-four hour studies result in four significant combinations, best illustrated by the following diagram which appears in the original article.



The authors conclude that the radioactive rose bengal test is safe and practical in the differential study of jaundice as well as in the study of liver function; that the peak liver radioactivity within forty-five minutes to ninety minutes is characteristic for the normal as contrasted with the abnormal and that the early and twenty-four hour values permit differentiation of the jaundiced patients; that the blood level is a mirror image of liver concentration; that both polygonal cell function and biliary patency are tested; and that it is necessary to obtain, simultaneously, liver and blood radioactivity levels both early and at twenty-four hours for maximum clinical usefulness of the examination.—*Daniel L. Rousseau, M.D.*

MENA, ISMAEL, BENNETT, LESLIE R., KIVEL, RAYMOND, SCALLON, JOSEPH, and MELLINKOFF, SHERMAN M. Determination of cardioportal circulation time by external scintillation counting. *Am. J. Digest. Dis.*, Jan., 1959, 4, 19–28. (From: Departments of Radiology and Medicine, University of California Medical Center, Los Angeles, Calif.)

A method for determining the cardioportal circulation time by utilizing radioiodinated human serum albumen and simultaneous external scintillation counting over the heart and liver is presented. A dose of 0.25 μc of radioiodinated human serum albumin per kilogram of body weight is injected intravenously. Recording is begun at the moment of injection and is concluded when a well defined plateau is reached over the liver. The cardiac and liver data are plotted on the same graph.

The appearance of radioactivity in the heart serves as a reference point. The peak of the curve occurs 10 to 12 seconds after injection in the absence of cardiopulmonary disease and is followed by an exponential decrease in activity. A rapid rise in activity over the liver occurs and gradually increases. The emptying of the hepatic sinusoids cannot be detected due to the activity in the portal vein. The portal curve begins 3 to 5 seconds after the hepatic artery curve and rises to a peak 25 seconds after the cardiac peak.

The present method does not measure absolute hepatic blood flow. Inferences can be made regarding the hepatic artery and portal vein blood flow and the mean cardioportal circulation time can be estimated. The cardioportal circulation time is the time from the peak of the cardiac curve to the peak of the portal curve.

The study included 87 cardioportal circulation times in 85 subjects. The mean cardioportal circulation time was 25 seconds in 36 normals. In 26 patients with portal cirrhosis, the time was 45 seconds. In 3 additional cases with cirrhosis and portal venous obstruction due to thrombosis, the time was 55 seconds. In 7 cases with cirrhosis and portacaval anastamoses the time was 19 seconds. In 2 cases with acute hepatitis there was an abrupt rise in the curve suggesting a large hepatic artery component. The cardioportal circulation time was slightly prolonged in obstruction of the common bile duct and was definitely prolonged in 2 cases of mitral stenosis in congestive failure. There were 5 patients in whom the cardioportal circulation time was determined and whose portal pressures were measured at the time of operation and there was a definite correlation between a prolonged cardioportal circulation time and the presence of increased portal pressure.

The above method is a valuable adjunct to the clinical diagnosis and study of hepatic circulation. —*Charles W. Cooley, M.D.*

BERKOWITZ, DONALD, SKLAROFF, DAVID, WOLDOW, ASHER, JACOBS, A. GERSON, and LIKOFF, WILLIAM. Blood absorptive patterns of isotopically-labeled fat and fatty acid. *Ann. Int. Med.*, Feb., 1959, 50, 247–256. (From: Departments of Medicine and Radiology, Albert Einstein Medical Center, Northern Division, the Hahnemann Medical College, and the Sidney Hillman Medical Center at the Male Apparel Industry, Philadelphia, Pa.)

I^{131} labeled triolein and oleic acid have been added recently to the older methods to study abnormal fat metabolism by biochemical measurements of specific blood constituents such as cholesterol, lipids or lipoprotein fractions and by intubation studies which quantitate pancreatic secretions and stool analyses. A fatty meal containing 25 μc of I^{131} labeled triolein or oleic acid is administered and venous blood samples are taken periodically until a maximum radioactivity level has been reached and again at twenty-four hours. The radioactivity in each sample as well as the twenty-four hour urine and stool collections are determined and expressed as a percentage of the activity of the initially ingested meal. The I^{131} circulates in the blood in the organic fraction attached to the lipoprotein molecule and in the inorganic fraction which is formed by fat catabolism. Normally the organic part does not exceed 50 per cent of the total. The blood radioactivity curves include (1) time of maximal blood radioactivity, (2) magnitude of the maximal value, (3) twenty-four hour activity level and (4) organic fraction/whole blood radioactivity ratio.

The mean whole blood radioactivity after ingestion of an I^{131} triolein test meal normally rises to a peak value of 11.7 per cent in six hours and then gradually declines at twenty-four hours to 2 per cent. The organic fraction represents less than 5 per cent of the total. The twenty-four hour urines contained usually 20 to 40 per cent of the administered dose and the fecal radioactivity was less than 2 per cent.

The above method is useful in the differential diagnosis of steatorrhea. A normal triolein curve rules out a major absorptive defect, whereas a flat curve and an elevated stool activity is indicative of malabsorption. This may be the result of a faulty digestion or of a primary mucosal defect. An I^{131} oleic acid meal can then be given and a normal blood curve indicates insufficient pancreatic lipase. A flat curve indicates an intestinal mucosal disturbance.

A normal I^{131} triolein curve in jaundice rules out any major obstructive process. A flat triolein curve and a normal oleic acid result indicate that insufficient quantities of pancreatic enzymes are present in the intestinal tract for normal absorption to occur. This could be due to pancreatic disease or common duct obstruction.

The degree of fat malabsorption can be studied in various conditions such as regional ileitis, Whipple's disease, gastrocolic fistula, subtotal gastrectomy and lymphosarcoma.

The authors found a marked decrease in fat absorption in patients with heart failure and a corresponding improvement with cardiac compensation. Unusually high peak blood levels of total and lipid blood radioactivity, delays in attaining these concentrations, and elevated twenty-four hour values were found in cases of coronary atherosclerosis and hypercholesterolemia.

It is believed that with modification of the above tests and a wider application in adjacent fields valuable information will be obtained in basic metabolic processes.—*Charles W. Cooley, M.D.*

Greenspan, Richard H., Lester, Richard G., Marvin, James F., and Amplatz, Kurt. Isotope circulation studies in congenital heart disease. *J.A.M.A.*, Feb. 14, 1959, *169*, 667–672. (From: Department of Radiology, University of Minnesota, Minneapolis, Minn.)

The difficulty in detecting right to left intracardiac and extracardiac shunts with cardiac catheterization, angiocardiography, and dye dilution curves is emphasized. The authors developed another procedure consisting of injecting 1 μc/kg. of I^{131} labeled sodium and methylglucamine diatrizoate, which serves as a rapidly excreted radioactive tracer (biologic half life of five hours versus three days for iodinated albumin). The injection may be made into various chambers at the time of catheterization. The venous route may also be utilized but is less accurate and is only recommended as a screening procedure. A collimated scintillation counter is placed over the heart, peripheral lung field and a femoral artery and the time of appearance of increased radioactivity is measured.

This method was used in 42 patients suspected of having right to left shunts. Other conditions may also be studied. In 17 patients with mitral valve disease investigated by this means there was a marked delay (up to twenty seconds as compared to a normal of five seconds) in the appearance of radioactivity in the femoral artery.

The apparatus needed can be reduced to a compact portable unit and the method has obviated the need of arterial puncture in the detection of intracardiac and extracardiac shunts.—*Eugene C. Klatte, M.D.*

Copenhaver, W. M. Distribution of radioactive sulfate in the heart of fetal, newborn, and adult rabbits. *Anat. Rec.*, Aug., 1958, *131*, 669–675. (From: College of Physicians and Surgeons, Columbia University, New York, N. Y.)

Distribution of S^{35} in the rabbit heart was studied in fetuses of age 14 days to birth, in young animals of age from one to ten days, and also in adults. The fetuses were exposed to the isotope by intravenous injection of the mothers seven hours prior to autopsy. Distribution of the tracer radiosulfur was determined by autoradiographs made by coating fixed sections with bulk emulsion. Autoradiographs were compared with histologic slides stained with periodic acid-Schiff or toluidine blue stains.

The resulting autoradiographic material is very interesting, and shows a clearly demonstrable uptake of S^{35} in the endocardial cushions of the atrioventricular junction and in the bulbus in the 14 day fetus, with

little deposition in the myocardium. In older fetuses heart valves, chordae tendinae and annuli fibrosi all show convincing selective localization of S^{35}, incorporated in chondroitin sulfate.

Uptake of S^{35} in the above structures increases with increasing fetal age into the newborn period. Within 10 days after birth selective localization decreases, and finally stabilizes, in the adult, at a turnover rate of once in six days.

This paper represents an intriguing example of the various applications of autoradiography to biologic problems.—*Frederic J. Bonte, M.D.*

Bonard, E. C., and Indemini, M. Anémies hyperchromes et vitamine B_{12} radioactive; Etude par la méthode de Schilling. (Hyperchromic anemias and radioactive vitamin B_{12}; Study using Schilling's test.) *Schweiz. med. Wchnschr.*, March 7, 1959, *89*, 251–255. (From: Policlinique universitaire de médecine, and Institut de radium, Genève, Switzerland.)

Three methods utilizing radioactive cobalt 60 labeled vitamin B_{12} are used in the investigation of hyperchromic anemia: Measurement of the stool radioactivity after ingestion of the tagged vitamin B_{12}; uptake of radioactive vitamin B_{12} by the liver (external counting); and the Schilling test.

The authors, using the original Schilling test in their work based on 35 cases, evaluate the results and discuss the usefulness of the method. Their results are as follows: 21 per cent and 33 per cent in 2 patients who were clinically normal; 10 per cent to 29 per cent in known cases of hypochromic anemia; and 0 to 3 per cent in patients with hyperchromic anemia, but without the use of the intrinsic factor. A figure of over 10 per cent was obtained in these latter cases after administration of the intrinsic factor. In 10 other cases not considered above, the results were not conclusive, with or without the use of the intrinsic factor.

Their results are exemplified by 10 interesting clinical cases. In studying anemias with radioactive vitamin B_{12}, the authors found that it was possible to confirm the diagnosis of pernicious anemia in a series of patients, even though they were in full remission.

In the whole group of hyperchromic anemias, the Schilling test also permits the discrimination of those caused by an intestinal absorption deficiency from those due to another avitaminosis (folic acid).

The authors review the current literature on the subject in the light of their experience and indicate the many possibilities of the test. Twenty-five references are given.—*Etienne LeBel, M.D.*

Kurland, George S., Golodetz, Arnold, Hamolsky, Milton W., and Freedberg, A. Stone. Thyroid function in supraventricular tachycardias: Turnover of intravenously infused I^{131}-labeled thyroxine and the red blood cell uptake of I^{131}-labeled *l*-triiodothyronine. *J. Clin. Endocrinol. & Metabol.*, Jan., 1959, *19*, 92–102. (From: Department of Medicine of the Harvard Medical School; the Medical Research Department of Yamins Research Laboratories and the Medical Service, Beth Israel Hospital, Boston, Mass.)

A group of 39 patients with supraventricular tachycardia was studied by means of tests relating to the peripheral metabolism of thyroid hormone. The usual tests showed all these patients to be euthyroid. The turnover rate of infused I^{131} thyroxine was significantly increased over that of other euthyroid patients, but less than for hyperthyroids. The average *in vitro* red blood cell uptake of I^{131} triiodothyronine was significantly elevated in the whole series, this test supposedly measuring the relative binding affinities of tissues for thyroid hormone. Several patients were treated with potassium iodide with striking clinical benefit and associated decrease in red blood cell uptake. Hypotheses are reviewed suggesting a selective sensitivity of the heart muscle to thyroid hormone.—*Patrick J. Cavanaugh, M.D.*

Fellinger, K., Egert, H., Höfer, R., and Vetter, H. Zur Problematik der Radiojodtherapie der malignen Struma. (Concerning the problems of radioiodine therapy of malignant struma.) *Wien. klin. Wchnschr.*, May 1, 1959, *71*, 309–314. (From: II. Medizinische Universitätsklinik, Vienna, Austria.)

In this article radioiodine therapy of malignant struma is discussed on the basis of 57 cases. Diagnostically, I^{131} offers the following four advantages: (1) It determines exact localization of thyroid tissue, which is especially important when distant metastatic lesions are suspected; (2) it shows the amount of retention of radioactive material; (3) the test may reveal abnormal values, even when most normal tissues have undergone destruction and thyroid function has been more or less eliminated; and (4) the medication renders possible autoradiography of biopsy specimens whereby the exact site of storage can be determined.

Therapeutic application cannot be effective unless sufficient storage of radioiodine has been assured. This storage has been definitive in only 15 cases, or 26 per cent of the series, and questionable in 3 (5 per cent). In the non-storing cases, the residual healthy thyroid tissue can be eliminated either by radioiodine medication or, preferably, by operation.

In planning therapeutic procedures one has to consider the following approach: (1) Surgery is always preferable in operable cases; (2) radioiodine

therapy is indicated in the inoperable cases, with or without metastatic foci, after all functional thyroid tissue has been eliminated either through surgery or medication of 80 mc I^{131}. In non-storing cases biopsy is necessary. When tissue sections show follicles filled with colloid material, the residual thyroid tissue can be eliminated; (3) the same considerations are valid for cases with incomplete strumectomy; (4) thyrostatic medication can also be tried and be followed by roentgen therapy; (5) for undifferentiated carcinoma and mesodermal blastoma, roentgen therapy is the method of choice. Single therapeutic doses of 100 to 300 mc I^{131} are recommended.

Reproductions of roentgenograms of 3 cases illustrate metastatic osteolytic bone lesions with complete restoration of structures following the medication. Four cases are briefly reported to show the variety of treatment planning.—*Ernest Kraft, M.D.*

Reinhard, Edward H., Neely, Charles L., and Samples, Don M. Radioactive phosphorus in the treatment of chronic leukemias: long-term results over a period of 15 years. *Ann. Int. Med.*, April, 1959, *50*, 942–958. (From: The Department of Medicine, Washington University School of Medicine, and Barnes Hospital, St. Louis, Mo.)

The authors review certain aspects of the results of treatment of chronic leukemias with radioactive phosphorus (P^{32}). Clinical material includes 102 patients with chronic lymphocytic leukemia and 118 patients with chronic granulocytic leukemia, all of whom received at least one course of treatment with radioactive phosphorus. Most, however, received treatment by at least one other modality, such as roentgen therapy or one of the chemotherapeutic agents. Of the latter, leukeran was used occasionally in the chronic lymphocytic group, while myleran, urethane and nitrogen mustard were used extensively in the chronic granulocytic group. Only a few patients in each group were treated with P^{32} alone. Also, it would appear that a number of patients with both diseases were seen in the same institution but not treated with P^{32}. No attempt is made to compare the findings in these patients with those in patients treated with radiophosphorus.

In the chronic granulocytic leukemia series, P^{32} was given intravenously, usually in several courses of treatment, in doses of 1.0 to 2.5 mc, at about two week intervals. A single course of treatment consisted of from 6 to 12 mc. If, following the administration of a total of 12 mc of P^{32}, the leukocyte count was still significantly elevated, the authors stopped treatment for several months before starting another course of the radioisotope. The average total dose was 21.8 mc with a range of 3.0 to 84.0 mc. Treatment was given whenever the leukocyte level rose above 50,000 cells per cubic mm., or when, with the leukocyte level between 25,000 and 50,000 cells per cubic mm., symptoms or distressing physical signs were present. Under special circumstances radioactive phosphorus was given when the leukocyte level was below 25,000 cells per cubic mm. It is interesting to note that in almost 50 per cent of all the patients in the chronic granulocytic series the hemoglobin increased at least 2 gm. as a result of treatment with P^{32}. In 24 per cent the hemoglobin increased more than 4 gm. per 100 ml. during treatment, without benefit of transfusion. A rise in platelet count was encountered in 2 of 8 patients whose initial platelet counts were less than 150,000. Five year survival, calculated against the "population at risk" at each yearly interval, was 12.5 per cent in this group.

The same criteria for treatment were used in the patients with chronic lymphocytic leukemia, although the average total dose was lower, 11.6 mc. Some authors do not tend to predicate the need for treatment upon the white blood cell level in chronic lymphocytic leukemia, since there is a good deal less relation between white blood cell count level and the clinical state of the patient than in chronic granulocytic leukemia. Five year survival, calculated on the basis of "population at risk," was 51 per cent.

Even though most of the patients reported in this paper received treatment by more than one modality, the results are valuable in helping to assess relative merits of the several available modes of therapy of the leukemias.—*Frederick J. Bonte, M.D.*

Fraser, R., Joplin, G. F., Laws, J. W., and Morrison, R. Needle implantation of yttrium seeds for pituitary ablation; in cases of secondary carcinoma. *Lancet*, Feb. 21 1959, *1*, 382–386. (From: Medical Research Council's Radiotherapeutic Research Unit, and the Departments of Radiotherapy, Radiodiagnosis, and Medicine, of Hammersmith Hospital and Postgraduate Medical School, London W.12, England.)

A relatively simple method of pituitary ablation by means of energetic beta irradiation from radioactive yttrium seeds is described. The seeds are implanted through a needle introduced into the fossa pernasally, position being controlled by the use of biplane image amplifiers.

Functional hypopituitarism was accomplished in 80 per cent of the cases. Visual field defects, rhinorrhea, and meningitis were described as complications arising when seeds were implanted too close to the diaphragma sellae.

Without regard to the value of pituitary ablation in advanced mammary cancer it would seem that this method, widely used in England, may become more generally applicable than surgery.—*P. J. Cavanaugh, M.D.*

Jakob, Alfons, and Dietrich, Günther. Unsere Ergebnisse mit der Radio-Strontium-

und Radio-Yttrium-Bestrahlung des Hämangioms und des Naevus flammeus. (Results of treating hemangiomas and flame nevi with radiostrontium and radioyttrium.) *Strahlentherapie*, Dec., 1958, *107*, 532–536. (From: Strahleninstitut der Städtischen Krankenanstalten, Nürnberg, Germany.)

Since 1954, treatment of 294 patients with 366 hemangiomas (287 simple hemangiomas, 60 cavernous hemangiomas, and 19 flame nevi) by strontium 90 skin plaques (320 fields), yttrium 90 sheets (28 fields) and radium (25 fields) has yielded essentially the same results as the previously employed radium therapy. Cosmetically, only 2 of the 287 hemangiomatous fields treated showed undesirable telangiectasis. Better results were obtained in treatment of the flame nevi than when thorium X was used.

Small fields were treated with strontium 90 plaques; larger fields with yttrium 90 sheets. Dosage was approximately 1,000 rep per treatment, repeated no earlier than in two to three months, to an average total dosage of 3,000–4,000 rep in a year. The intensity of radiation from the plaques and sheets was measured with a Siemens phantom chamber.

The authors consider a subcutaneous position of a hemangioma to be a contraindication for this type of treatment. They consider treatment of the more superficial hemangiomas with radium contraindicated because of the potential genetic hazard.—*Henry G. Moehring, M.D.*

Cocchi, Umberto. Apparat zur Einführung von Radiokobaltlösungen in die Harnblase. (Apparatus for introducing radiocobalt solution into the urinary bladder.) *Strahlentherapie*, Feb., 1959, *108*, 293–295. (From: Radiotherapeutische Klinik der Universität, Zürich, Switzerland.)

This is a fairly detailed description of an apparatus used to instill a solution of radioactive cobalt into a balloon in the urinary bladder for the treatment of noninfiltrating, superficial tumors and papillomas of the bladder. The operator is shielded from the solution by a 5 cm. layer of lead.—*Henry G. Moehring, M.D.*

Pierce, John A., Reagan, W. Paul, and Kimball, Robert W. Unusual cases of pulmonary arteriovenous fistulas, with a note on thyroid carcinoma as a cause. *New England J. Med.*, April 30, 1959, *260*, 901–907. (From: The Department of Medicine, University of Arkansas Medical Center, Little Rock, Ark.)

This article is of interest chiefly because it includes a description of a case of abnormal arteriovenous shunt apparently occurring in the vessels serving multiple large pulmonary metastases from a primary carcinoma of the thyroid gland. Evidence of the abnormal communication, in the form of characteristic symptoms and signs, began abruptly when the patient was seventeen years old, shortly before he was found to have a carcinoma of the thyroid gland with roentgenographic evidence of hematogenous pulmonary metastases. A course of radiation therapy to the thyroid region controlled the primary tumor and, during a period of seven years thereafter, the pulmonary metastases remained unchanged except for calcium deposition within several of them. When the patient attained the age of twenty-four, seven years after he had first been seen, I^{131} tracer studies revealed specific uptake of radioiodine by the tumor nodules in the lungs, as demonstrated by an interesting scintillation scan reproduced in this paper. Treatment of the metastatic lesions with large doses of I^{131} caused an apparent slight reduction in volume of the metastatic deposits in the lungs, and improved arterial hemoglobin oxygen saturation.

The authors theorize that, because of the sudden onset of symptoms at the time the metastatic tumor was first identified and because of the favorable response in reduction of tumor volume by radioisotope therapy, the abnormal shunts existed in vessels serving the tumor metastases.—*Frederick J. Borte, M.D.*

Crile, George, Jr., and Wilson, Donald H. Transformation of a low grade papillary carcinoma of the thyroid to an anaplastic carcinoma after treatment with radioiodine. *Surg., Gynec. & Obst.*, March, 1959, *108*, 357–360. (From: Department of General Surgery, The Cleveland Clinic Foundation and The Frank E. Bunts Educational Institute, Cleveland, Ohio.)

This is a case report of a low grade papillary carcinoma, quiescent for thirty-four years, but apparently transformed into a highly undifferentiated, rapidly growing, autonomous cancer following a period of myxedema induced by treatment with I^{131}. This is the fourteenth case of this type to be reported.

It is the authors' belief that the increased output of thyroid stimulating hormone induced by the treatment with I^{131} either initiated the transformation of the cancer to an undifferentiated and autonomous type or promoted the growth of dormant cancer cells.

The authors strongly urge that patients with inoperable differentiated thyroid cancers be given a trial of treatment by feeding desiccated thyroid before administering I^{131} or that roentgen therapy be used. They also urge that operable papillary carcinomas be removed, even though apparently stationary, for they believe it possible that some of them

undergo change to a more malignant type.—*George Tievsky, M.D.*

Ernst, Helmut, Iglauer, Eduard, Kronschwitz, Helmut, and Spode, Ernst. Tierexperimentelle Untersuchungen zur Frage der Therapie von Lungentumoren mit Hilfe radioaktiver Gold-Kohle-Suspensionen. (Carbon suspension of radioactive gold in animal experiments in the treatment of pulmonary tumors.) *Strahlentherapie*, Nov., 1958, *107*, 382–390. (From: Institut für Medizin und Biologie der Deutschen Akademie der Wissenschaften zu Berlin, Berlin, Germany.)

From 1–22.5 mc of colloidal radioactive gold adsorbed on activated (wood) carbon particles and suspended in 50 ml. of 20 per cent glucose solution were injected through a cardiac catheter into lobar or segmental pulmonary arteries of 18 dogs. When the physical preparation of the suspension was controlled so that the carbon particles were 40–50 μ in diameter, good localization of radioactivity to the selected segment was obtained with only relatively small amounts in the liver and spleen and in other segments of the lungs. Despite the use of small total doses, the intensity and duration of radioactivity in the selected segments was sufficient to be counted of therapeutic moment. The radioactivity in the spleen and liver was not proportional to the amount of carbon lodged in these organs; hence, some de-adsorption of the radioactive gold must have occurred *in vivo*. Further investigations are under way to explain the mechanism of this de-adsorption. Change of temperature of the suspension from that of the room to that of the dog's body is a partial explanation, but some additional "biologic de-adsorption" seems also to take place.—*Henry G. Moehring, M.D.*

Spode, Ernst, Gensicke, Friedrich, and Glaser, Roland. Untersuchungen über das Verhalten von Radioholmium (^{166}Ho) im Organismus der weissen Maus. (Distribution of radioactive holmium [Ho^{166}] in white mice.) *Strahlentherapie*, Jan., 1959, *108*, 97–101. (From: Institut für Medizin und Biologie der Deutschen Akademie der Wissenschaften zu Berlin-Buch, Berlin, Germany.)

Holmium 166 is one of the heavy rare earths with a half life of 27.3 hours and an $E_{\beta max}$ of 1.84 mev. and E_γ of 1–4 and 0.08 mev. Dissolved in a saline solution (specific activity of 3,460 mc per gm.), 0.2 ml. yielded 100 μc at a pH of 3.0. This dose was injected subcutaneously or intraperitoneally in 56 male and female mice that weighed between 13 and 20 gm. The mice were sacrificed at one, three, six and twenty-four hours, and at three and six days after the injection.

Subcutaneously injected holmium 166 was poorly absorbed so that even at six days 97.4 per cent of the dose remained at the injection site. Intraperitoneal injection resulted in better absorption, but even then most of the injected dose remained in the peritoneal cavity. Excretion is largely by way of the liver and bile; only a small amount is excreted through the kidneys. These observations indicate that holmium 166 might be suitable for interstitial tumor therapy.—*Henry G. Moehring, M.D.*

CHEMOTHERAPY

Flosi, A. Z., Assis, L. M., Coelho Neto, A. S., Bloise, W., Ulhôa Cintra, A. B., and Barros, R. P. Hormonal treatment of Hand-Schüller-Christian disease: Report on a case with disappearance of the bone lesions. *J. Clin. Endocrinol. & Metabol.*, Feb., 1959, *19*, 239–247. (From: Department of Metabolism and Endocrinology, Hospital Das Clinicas, São Paulo University, São Paulo, Brazil.)

A case is reported of Hand-Schüller-Christian disease which was treated with cortisone and ACTH.

The diagnosis was established when the patient was one year old by biopsy examination of a lesion found behind his left ear. Roentgenograms at that time showed numerous osteolytic lesions in the skull, maxilla, spine, innominate bone, and right femur.

Cortisone and ACTH were given therapeutically with remarkable clinical improvement and with definite reduction in the size and healing of the lesions. When the hormones were omitted for a short period of time, a deterioration in the patient's clinical condition was observed with re-exacerbation of the bone lesions. After one year's treatment with cortisone and ACTH, the addition of estrogens and desiccated thyroid was made to stimulate osteoblastic activity and bone reconstruction.

After two years' time a satisfactory resolution of the disease was achieved. The hormones were well tolerated with the exception of the following observations: Cushingoid features which had developed in the second year disappeared upon reduction of the ACTH dosage. Gynecomastia which appeared during estrogen therapy had persisted up to the present period. A pronounced advance in the bone age occurred following addition of estrogen and thyroid to the therapeutic regimen.

The authors re-emphasize the possibility of success in hormonal treatment of Hand-Schüller-Christian disease. Nine months have elapsed since all therapy was discontinued in this patient with complete absence of any clinical or roentgen manifestations of the disease. Roentgenograms show complete disappearance of lytic lesions and return of normal bone structure. Total remission of the bone lesions has lasted four years.—*Bernard S. Loitman, M.D.*

MISCELLANEOUS

Mahlo, A. Über den Wert und die Technik der Saugbiopsie des Magens. (The value and technique of suction biopsy of the stomach.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Feb., 1959, *90*, 165–171. (Address: Lilienstr. 36, Hamburg, Germany.)

The technique of suction biopsy of the stomach controlled by roentgen examination is described. The device constructed by the author is a gastric tube with a metallic head containing an opening for the small biopsy knife. After careful fluoroscopic placement of it against the inspected gastric segment, a small fragment of gastric mucosa is sucked into the biopsy opening and removed by the small cutting knife.

The author has done more than 1,000 such mucosal biopsies without complications or bleeding of consequence. The biopsy can be done after the questionable lesion is outlined by a small amount of contrast material. All portions of the stomach except the high fundus are easily accessible for this method. It has been a very valuable and safe procedure in the hands of the author.—*Hans W. Hefke, M.D.*

Woolner, Lewis B., McConahey, William M., and Beahrs, Oliver H. Struma lymphomatosa (Hashimoto's thyroiditis) and related thyroidal disorders. *J. Clin. Endocrinol. & Metabol.*, Jan., 1959, *19*, 53–83. (From: Sections of Surgical Pathology, Medicine, and Surgery, Mayo Clinic and Mayo Foundation, Rochester, Minn.)

This paper is an exposition of the results of a clinicopathologic study of 605 cases of thyroiditis of the "Hashimoto" type seen at the Mayo Clinic over a twenty-seven year period. Clinical and laboratory data are presented according to the following classification of these cases: The morphologic grouping includes diffuse thyroiditis (188 cases); thyroiditis with "hyperplastic" epithelium (57 cases); and focal thyroiditis (360 cases). There is a further histologic subgrouping of the diffuse thyroiditis cases: 29 cases with extensive epithelial destruction; 36 cases with oxyphilic epithelium; 106 cases with varied epithelial changes; and 17 cases with severe lymphoid infiltration or associated lymphosarcoma (considered *in toto*, these subgroups represent an advanced stage of the disease).

In addition to detailed findings, the authors discuss the results of thyroidal function tests for a limited number of cases in each category. They also specify the 18 cases of associated carcinoma and the 12 cases of associated lymphosarcoma which were included in their 605 cases. They found that, in these instances, there was definite invasion of adjacent parenchyma, although all were papillary and of low malignancy.—*James A. Martin, M.D.*

Jellinek, Stefan. Immediate effects of irradiation of elastic tissues with x rays, radium, and radioactive cobalt. *Lancet*, Nov. 29, 1958, *2*, 1149–1151. (Address: S. Jellinek, Professor of Electropathology, University of Vienna, Vienna, Austria.)

Experiments have been performed on the effects of electricity on elastic tissues, but little has been done on the radiation effects. This experimental work using irradiation has been carried out on the ligamentum nuchae of 10 calf fetuses and also on the skin of 5 recently deceased human corpses.

Irradiated portions of the ligamentum nuchae of the calf fetuses showed a wide range of morphologic changes varying from slight curling and spur formation to disruption and dislocation of the majority of the fibers and occasionally complete fragmentation. The elastic fibers were swollen and their staining capacity impaired, suggesting a physiochemical mechanism as well as a mechanical action of irradiation.

Roentgen rays, radium and radioactive cobalt in quantities ranging from 1 r to 50,000 r were used. Changes were found in all experiments and the threshold seemed to lie outside the range examined, *i.e.*, below 1 r.—*Frank J. Rigos, M.D.*

Trout, E. Dale, Kelley, John P., and Lucas, Arthur C. Broad beam attenuation in concrete for 50 to 300-Kvp x-rays and in lead for 300-Kvp x-rays. *Radiology*, Jan., 1959, *72*, 62–67. (Address: E. D. Trout, 4855 Electric Ave., Milwaukee 1, Wisc.)

It is difficult to obtain data for broad beam roentgen-ray attenuation in concrete. Large fields of at least 3 feet in diameter at the barrier must be used to obtain the data. Concrete sheets of this size, especially since they must also be thin for the low kv. peak range, are not easily constructed or handled. It is possible, however, to obtain attenuation data in another material of low atomic number and, by applying the necessary corrections for differences in density, atomic number and weight, to obtain data for concrete. In the present study, aluminum was used because its physical factors compare closely to those of concrete. The correction factor was found to be 1.11. Thus, for any given aluminum thickness, the equivalent concrete thickness can be obtained by multiplying the aluminum thickness by 1.11. A plan of the geometric arrangement of the experimental apparatus is shown. Attenuation data are given in graphic form for roentgen-ray energies between 50 and 300 kv. peak in terms of concrete thickness. Voltages and filtrations were selected to coincide with attenuation data given in N.C.R.P. Handbook

60. Occasionally, it may be desirable to add lead to an existing concrete barrier to obtain the desired lead equivalent for the composite barrier. A table of various concrete and lead equivalents is presented. The data are derived from the curves for lead in Handbook 60 and the curves for concrete obtained in the present study.

Broad beam attenuation data in lead for 300 kv. peak pulsating wave sources have not been previously available. Handbook 60 data for 300 kv. lead attenuation are based on a constant potential source. A table showing the authors' attenuation data for 250 and 300 kv. peak (pulsating) along with 250 kv. peak (pulsating) and 300 kv. (constant), obtained from Handbook 60, is presented.—*Z. Petrany, M.D.*

Kirkpatrick, John A., Jr. Fluoroscopy in pediatric radiology and the implications of image intensification. *Radiology*, Dec., 1958, *71*, 823–825. (Address: St. Christopher's Hospital for Children, Philadelphia 33, Pa.)

Fluoroscopy, especially in pediatric radiology, is a potentially hazardous procedure because of the amount of radiation exposure which is involved in its use. However, the nature of certain disease processes in early life makes fluoroscopic examination of relatively more value in this age group than in adults. Acute inflammatory disease of the lung in an infant may be first manifested by obstructive emphysema, which is difficult or impossible to recognize on roentgenographic studies. Congenital lesions of the tracheobronchial tree, the pulmonary parenchyma, and the heart and great vessels can often be best assessed fluoroscopically. This is true also in evaluating esophageal function, and under certain circumstances small bowel and colonic lesions can best be diagnosed by careful fluoroscopic study.

The advent of the image intensifying screen allows these studies to be done with considerably less exposure and at the same time offers other advantages which the conventional machine does not have. Since a lighted room can be used, it makes for a much more cooperative child. Procedures such as bronchography, injection of sinus tracts, or procedures which necessitate anesthesia are more readily done under these circumstances. The brighter image makes possible the technique of cinefluorography whereby the functional activity of the gastrointestinal and cardiovascular systems can be better analyzed both in disease and health. It is pointed out, however, that even these techniques may be abused, and the use of ionizing radiation as a diagnostic tool in pediatrics must be carefully evaluated in every instance.—*Z. Petrany, M.D.*

Gorson, Robert O., Halvorsen, Ronald M., Lieberman, Jesse, and Aitken, Edward V. A limited survey of radiation exposure from dental x-ray units. *Radiology*, Jan., 1959, *72*, 1–13. (Address: R. O. Gorson, 3400 Spruce St., Philadelphia 4, Pa.)

As a part of its expanding program in radiation hazard control, the Department of Public Health of the City of Philadelphia instituted in 1956 a study of radiation exposure from various medical roentgen-ray units. Reported in this paper are the results of measurements made on 56 dental roentgen-ray units. All calibrations and radiation surveys were performed under the operating conditions normally employed by the dentist in charge.

This study showed that the radiation exposure to the dentists and their assistants was on the average considerably less than 100 mr per week, the accepted maximum permissible average weekly dose. However, the fact that many dentists received very low radiation exposures indicates that others could improve on theirs. It is suggested that operating tube potentials and added filter combinations be used to decrease the "soft" radiation that many were found to have. A half-value layer preferably greater than 2.0 mm. Al and not less than 1.8 mm. Al is recommended for the primary beam to do this. The primary beam diameters at the tip of the cone were found to be larger than necessary in about one half of the units. A diameter of not more than 3.0 inches and preferably less than 2.5 inches is recommended. Radiation exposure to the patient was found to range from 0.4 to 15.8 r (in air at the skin) for periapical roentgenograms.

It is felt that with proper filtration and tube potentials together with good technique and materials, the exposure dose to the patient should be reduced to an average of 3.0 r for a periapical molar roentgenogram. The authors suggest that a further comprehensive and objective study of roentgenographic dental techniques is indicated in order to reach the goal of ideal dental studies with a minimum of exposure to the patient and to office personnel.—*Donald N. Dysart, M.D.*

Björnerstedt, R., and Engström, B. Maximum permissible body burden of strontium-90. *Science*, Feb. 6, 1959, *129*, 327–328. (From: Research Institute of National Defense, Stockholm, Sweden, and Department of Medical Physics, Karolinska Institutet, Stockholm, Sweden.)

This article, representing Part 3 of a series on health hazards from fission products and fallout, deals with the derived dose rates produced by bone seeking isotopes. Sr^{90} is used as an example to illustrate a proposed method for estimating the maximal permissible body burden.

The authors calculate that, while the accepted maximum value of 1 μc Sr^{90} produced dose rates of 5.5 to 9 mrem/day (average 7.25 mrem/day) in bone,

there are, because of increased concentration of Sr^{90} in areas of reactive bone, microscopic areas in adult bone which may receive as high as 300 to 500 mrem/day. Assuming that bone and blood malignancies result from local microscopic conditions and that a dose of 1,000 rem over a long period of time is significant in producing biologic damage to bone, a body burden of 1 μc Sr^{90} may produce dangerous doses in small areas of bone over a ten year period. This suggests a revision of the maximum permissible body burden of from 1.0 μc to 0.1 μc Sr^{90}.

The above estimates are based on short-time or "acute" poisoning with Sr^{90}. If Sr^{90} is taken into the body over a longer period of time, the pattern of isotopic localization is different. Such "chronic" poisoning conditions prevail for children, since most calcium available in the biosphere is, and will be, contaminated with Sr^{90} from weapon tests.

The distribution of Sr^{90} tends to be more homogeneous, however, and 1 μc Sr^{90} in 7,000 gm. of bone is estimated to produce doses of radiation of from 1.5 to 15 mrem/day, the average being 7.25 mrem/day. Moreover, the biologic half life is also considered, reducing the effective half life to 7.4 years. The authors therefore conclude that the total body burden in the case of chronic poisoning may be higher than 0.1 μc, tentatively 1.0 μc. With the Sr^{90} contamination in the geosphere and biosphere steadily increasing, the situation lies somewhere between acute and chronic Sr^{90} poisoning. Children up to five years of age are examples of chronic poisoning and adults above twenty years are more likely to be examples of acute poisoning.—*Daniel L. Rousseau, M.D.*

Wolman, Abel. Radiation and the health officer. *Yale J. Biol. & Med.*, Feb., 1959, *31*, 231–246. (From: School of Hygiene and Public Health, The Johns Hopkins University, Baltimore, Md.)

The author discusses the problems of radiation to man as related to exposure from natural sources, diagnostic radiology, accidents in operation of nuclear reactors, disposal of waste products of nuclear fission and the transportation of these products.

The administrative implications of control and regulation are discussed. Supervision in every hospital can be attained by establishing a Radiation Protection Committee as part of the hospital staff. Supervision of the medical uses of radiation outside the hospital, however, is not as simple.

The general problem can be supervised on a local and state level by the Public Health Department after appropriate legislation and training of the Public Health Department. On the international level, all officials are searching for appraisal, understanding and agreement between nations as to the management of this new material, its processing and effects.—*Frank J. Rigos, M.D.*

Alpen, Edward L., and Jones, D. M. Effects of concomitant superficial x-radiation upon the lethal effectiveness of 250-kvp. x-rays. *Radiology*, Jan., 1959, *72*, 81–85. (Address: E. L. Alpen, U. S. N. Radiological Defense Laboratory, San Francisco 24, Calif.)

A measurement for predicting the biologic effectiveness of ionizing radiation in a system which has not received a homogeneous dose is still a problem of radiation dosimetry. For the end-point of lethality in mammals, the dose which probably reflects the biologic damage most directly is that which is absorbed within the bone marrow. If this is true, radiation not capable of penetrating the shielding bony structures cannot accomplish biologic damage that would contribute to acute lethality.

In order to test the above hypothesis, dogs were irradiated with 1,000 r or 3,000 r total of 50 kvp. radiation, delivered bilaterally, followed by graded doses of 250 kvp. radiation (160 r to 240 r), or only graded doses of 250 kvp. radiation (260 r to 323 r) without any 50 kvp. radiation. The mortality data were analyzed by the method of maximum likelihood to arrive at estimates of the LD_{50} and the slope of the probit regression line.

From the data presented no significant conclusions can be drawn with respect to predicted biologic effectiveness from the air dose, surface dose, or integral dose. The midline tissue dose gives relatively good correlation between equi-effective exposures of the mixed radiations at the 1,000 r added 50 kvp. level. However, for the 3,000 r added 50 kvp. radiation a significant departure from the expected value is seen. The differences reflect the effect of bone attenuation on that portion of the lower energy radiation that reaches critical regions. In any case, these differences are small, considering the magnitude of the applied surface dose, and are sensitive to the variability in animal size. The differences, too, are ineffective in bone marrow destruction. The use of the midline tissue dose for roentgen-ray energies of 250 kvp. and above has been recommended previously to characterize bilateral exposures such as those used in this experiment.

In addition to bone marrow, the other radiosensitive tissue which must be considered is the gastrointestinal tract. No significant gastrointestinal effects resulted from this exposure of the whole gut to doses ranging from 250 to 1,550 rads. It is concluded that the intact function in the lesser irradiated portions was capable of preventing the effects which would have resulted from irradiating the entire gut at the higher dose level. This supports the work of other investigators that shielding of only a very small portion of the gut in the rat successfully prevents development of the gastrointestinal syndrome. These studies also indicate that, at least in this range of skin doses, no significant reduction of the LD_{50} en-

sues as the result of the surface irradiation.—*Walter H. Jarvis, Jr., M.D.*

Plenk, Henry P., Fuson, Roger, and Sorensen, Fred M. The nature of the effect of ACTH and cortisone on tumor growth in irradiated animals. *Radiology*, Jan., 1959, *72*, 75–80. (Address: H. P. Plenk, St. Mark's Hospital, Salt Lake City 16, Utah.)

The authors report the mutual effects of the concomitant use of ACTH or cortisone with irradiation on tumor bearing mice. Transplantation of tumor fragments (C-1300 neuroblastoma, 15091-a mammary carcinoma, and E-0771 mammary carcinoma) produced almost 100 per cent "takes" when placed into the anterior chamber of the right eye of ABC and C57B1 strains of mice. The tumor was readily seen in the anterior chamber three days after the transplant. ACTH (0.5 mg.) or cortisone (0.25 mg.) was administered daily intraperitoneally after the tumor inoculation, but prior to irradiation and was continued for fourteen, twenty, or forty-five days in those animals scheduled to receive steroids. A single dose of 3,000 r in air was administered through an 0.8 cm. field to the right orbit on the fourth day after transplant to those animals scheduled for irradiation. Recurrent tumor growth usually was apparent by the thirty-fifth day and led to death by the seventieth day. Those animals surviving the seventy day period of observation were usually found to be free of tumor.

In the unirradiated animals progressive tumor growth involved the orbit and frequently spread into the surrounding facial tissues. Most unirradiated control animals were dead by the fifty-sixth day. The single administration of 3,000 r (air) produced seventy day survivals of 23–55 per cent of the mice depending on the tumor type. The administration of ACTH or cortisone for at least fourteen days in conjunction with the single irradiation resulted in an increase in the seventy-day-survival rate in all 3 of the tumors. Cortisone was found to be more effective in the C-1300 neuroblastoma and E-0771 mammary carcinoma and ACTH more effective in the 15091-a mammary carcinoma. In the only tumor that regularly metastasized to the cervical lymph nodes (C-1300 neuroblastoma), ACTH and cortisone both produced a significant decrease in the incidence of metastases when administered to irradiated animals. ACTH and cortisone alone produced no demonstrable inhibitory or enhancing effect on the tumor growths, and no ill effects on the animals were noted.

The authors conclude that the prolongation of life and decreased incidence of metastases in hormone treated, irradiated animals is due to a modification of the effect of the irradiation by the steroids and not to direct action on the tumor growth.—*John S. Alexander, M.D.*

Danzker, M., Kessaris, N. D., and Laughlin, J. S. Absorbed dose and linear energy transfer in radiation experiments. *Radiology*, Jan., 1959, *72*, 51–61. (Address: M. Danzker, 444 E. 68th St., New York 21, N. Y.)

In most radiation experiments it is important to have both a quantitative measure of the amount of radiation involved and a qualitative description of the radiation which uniquely defines its significant properties. The required quantitative measure is the absorbed dose, which is the amount of energy absorbed per unit mass of the irradiated material. This can be expressed in rads (1 rad = 100 ergs/gm.). The most pertinent qualitative description is that of the spatial distribution of the collisions by which the electrons (or other ionizing and exciting particles) which are responsible for the actual energy dissipation lose their energy. This concept has been termed "linear energy transfer" (LET) and is defined in terms of the energy lost per unit path length by the particle. The LET is usually written as a function, L(T), of the kinetic energy, T, of the particle and is conveniently expressed in units of kev./μ where μ is 1 micron of path length. The significant information concerning the distribution of LET in the interior of the irradiated medium is given by the total amount of tract involved per unit LET interval. The distribution of tract length as a function of LET will then be n(L), which is really the ionizing particle flux written as a function of L(T) instead of the particle kinetic energy T.

The calculations presented in this paper are concerned with the methods of obtaining the absorbed dose D from cavity ionization measurements, and with the evaluation of the LET distribution function n(L). The calculations have been made for 7 continuous photon spectra with peak energies from 130 kev. to 22.5 mev., and for cobalt 60 gamma rays. Conversion factors to obtain the absorbed dose in rads in various materials from measurements in terms of the roentgen are presented.

This highly technical article, with its references to other original work in this field, the mathematical derivations, and numerous graphic illustrations, must be read and studied in detail by those who are interested in the subject.—*Walter H. Jarvis, Jr., M.D.*

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